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Pamam Dendrimer-Based Nano carriers for Solubility Enhancement of Etoricoxib

Aruna Moorthy[1*], Gokulakrishnan Kaliyamoorthy[2], Ketrin Jenowa Baskar[3], Sadvinaya Velusamy[4], Santhosh Basker[5], Srilakshmanan Murugesan[6]

[1]Department of Pharmacy Practice, [2,3,4,5,6] Department of Pharmaceutics, Sir Issac Newton College of Pharmacy, Nagapattinam, Tamilnadu-611102.

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Abstract: One way to achieve optimal delivery mechanisms for poorly soluble pharmaceuticals is to use PAMAM dendrimers. PAMAM dendrimers offer a variety of functional groups that can be used to aid in solubility by way of hydrogen bonds, electrostatic forces, encapsulation, or other means. In addition, PAMAM dendrimers contain numerous voids that may also assist with solubility through the aforementioned means PAMAM dendrimers can also be used effectively as a nanocarrier system to increase the solubility or bioavailability of hydrophobic drug molecules. PAMAM dendrimer drug delivery systems will be discussed in this review article, including their effect on enhancing solubility and pharmacokinetics of the drug Etoricoxib. To illustrate this point, the article will provide information about Etoricoxib's physicochemical properties, challenges encountered when developing drug formulations that will maximize Etoricoxib's therapeutic benefit, general characteristics associated with the construction of PAMAM dendrimers (including generation), how PAMAM dendrimers interact with drugs, previously published studies describing the use of dendrimers to facilitate solubility for poorly soluble drugs, and formulation approaches for creating Etoricoxib-dendrimer complexes and characterizing those complexes.

Keywords: PAMAM dendrimers, Etoricoxib, Nanocarrier drug delivery, Solubility enhancement, Dendrimer-based drug delivery systems, Poorly water-soluble drugs, COX-2 inhibitors, Pharmaceutical nanotechnology.

1. INTRODUCTION:

Many therapeutics have limited solubility in water, which can hinder the development of formulations with both efficacy and safety profiles. Multiple new therapeutic compounds have limited water solubility, which can result in poor dissolution and subsequently poor oral bioavailability due to low amounts of active pharmaceutical ingredient being absorbed after oral dosing [1,2]. Research and development in many pharmaceutical companies continue to focus on improving methods to increase the solubility of poorly soluble drug compounds, as improved solubility significantly influences drug absorption and the overall therapeutic effect [3]. To improve solubility, several widely accepted approaches have been developed, including the use of solid dispersions, particle size reduction, complexation techniques, and lipid-based drug formulations. However, these approaches may also have disadvantages such as instability of the final drug product, difficulties in manufacturing, and unpredictable improvements in bioavailability compared to the original formulation [4, 5].

Nanotechnology has made significant progress in improving the dissolution and delivery of poorly water-soluble drugs in recent years [6, 7]. One of the drug delivery systems that has emerged is a nanocarrier known as dendrimers. Dendrimers are unique, highly branched nanosized macromolecules with a well-defined and precise structure consisting of:

a) A central core

b) Repeatedly branched units

c) Numerous terminal functional groups [8]

Because of their architecture, dendrimers possess internal cavities capable of encapsulating hydrophobic drug molecules, while their surface functional groups can enhance solubility and facilitate interactions with biological systems [9]. Consequently, dendrimers have gained considerable attention as promising carriers for improving the solubility, stability, and bioavailability of poorly soluble drugs [10]. Among various dendrimers, poly (amidoamine) (PAMAM) dendrimers are one of the most extensively studied types in pharmaceutical nanotechnology. PAMAM dendrimers are characterized by their highly controlled molecular size and structure, providing a large number of surface functional groups and a high capacity for drug encapsulation or conjugation. The internal cavities of PAMAM dendrimers can entrap hydrophobic drug molecules, while the amino or other functional groups present on the surface can interact with drug molecules through hydrogen bonding or electrostatic interactions. These interactions make PAMAM dendrimers highly effective in enhancing the solubility and dissolution rate of poorly soluble drugs [11].

The anti-inflammatory and analgesic drug Etoricoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, exerts its pharmacological effect by reducing the formation of prostaglandins. Prostaglandins are inflammatory mediators produced from arachidonic acid through the action of cyclooxygenase enzymes. By selectively inhibiting COX-2, Etoricoxib suppresses prostaglandin synthesis, thereby reducing pain, inflammation, and fever associated with various inflammatory disorders [12, 13].

However, Etoricoxib exhibits poor aqueous solubility, which can prolong the time required for the drug to dissolve after oral administration and may limit its rate of dissolution and subsequent absorption [14]. Due to this limitation, several formulation strategies have been explored to improve its solubility and dissolution characteristics. Researchers have proposed advanced drug delivery systems such as solid dispersions, inclusion complexes, nanosuspensions, lipid-based formulations, and dendrimer-based nanocarriers to enhance the solubility and bioavailability of Etoricoxib [15].

Among these approaches**,** poly (amidoamine) (PAMAM) dendrimers have gained considerable attention as promising nanocarriers. PAMAM dendrimers possess a highly branched three-dimensional architecture with numerous terminal functional groups that provide a large surface area capable of interacting with different types of drug molecules. Hydrophobic or poorly soluble drugs can interact with the amine functional groups located on the surface of dendrimers through electrostatic interactions, hydrogen bonding, or even covalent conjugation, thereby improving their aqueous solubility and stability [16].

Dendrimers, particularly PAMAM dendrimers, have therefore been extensively investigated for their ability to serve as nanocarriers that enhance the chemical, biopharmaceutical, and pharmacokinetic properties of poorly soluble drugs. Drug molecules may be incorporated within the internal cavities of dendrimers or associated with their surface functional groups, which can significantly increase drug solubility and modify drug release characteristics from conventional dosage forms [17].

Consequently, the application of PAMAM dendrimers for the delivery of Etoricoxib represents a promising strategy to overcome its solubility limitations and enhance its oral bioavailability. This review focuses on the fundamental principles of dendrimer nanotechnology, the physicochemical characteristics of Etoricoxib, the mechanisms by which dendrimers improve drug solubility, and the advantages of dendrimer-based drug delivery systems for improving the formulation and therapeutic performance of poorly soluble drugs such as Etoricoxib [18].

2. OVERVIEW OF ETORICOXIB:

Etoricoxib (a non-steroidal anti-inflammatory drug, NSAID) is a selective cyclooxygenase-2 (COX-2) inhibitor that provides a newer class of pain-relieving medication. It was developed for the treatment of painful and inflammatory musculoskeletal conditions such as osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and acute gouty arthritis. Unlike conventional NSAIDs that inhibit both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), Etoricoxib selectively inhibits COX-2, thereby reducing inflammation and pain while minimizing gastrointestinal adverse effects commonly associated with COX-1 inhibition [19].

Etoricoxib possesses a bipyridine-type chemical structure with the molecular formula $C_{18}H_{15}ClN_2O_2S$ and a molecular weight of approximately 358.8 g/mol**.** It appears as a white or off-white crystalline powder and is practically insoluble in water but soluble in many organic solvents [20]. Due to its low aqueous solubility and high membrane permeability**,** Etoricoxib is classified as a Biopharmaceutics Classification System (BCS) Class II drug, where drug absorption is primarily limited by dissolution rather than permeability [21]. Consequently, its poor aqueous solubility may result in reduced dissolution rate and limited bioavailability in aqueous biological environments [22].

Etoricoxib selectively inhibits cyclooxygenase-2 (COX-2), an enzyme responsible for converting arachidonic acid into prostaglandins that mediate pain, inflammation, and fever. By inhibiting prostaglandin synthesis, Etoricoxib effectively reduces inflammatory responses and alleviates pain. Because of its selective inhibition of COX-2 rather than cyclooxygenase-1 (COX-1), Etoricoxib is associated with a lower risk of gastrointestinal adverse effects compared with traditional non-steroidal anti-inflammatory drugs (NSAIDs) [23].

Etoricoxib is administered orally and is rapidly absorbed into the systemic circulation. It demonstrates good oral bioavailability and is typically administered once daily due to its relatively long elimination half-life. The drug is primarily metabolized in the liver by cytochrome P450 enzymes, while its metabolites are eliminated mainly through urine and feces [24].

Despite its favourable pharmacological properties, the low aqueous solubility of Etoricoxib limits its application in pharmaceutical development, particularly in oral dosage forms. Poor solubility results in a slower dissolution rate in aqueous media, which can affect the rate and extent of drug absorption following oral administration. Therefore, improving the solubility and dissolution behaviour of Etoricoxib has become an important area of research in pharmaceutical formulation and drug delivery science [25].

Several formulation strategies have been investigated to enhance the solubility of Etoricoxib. These include solid dispersions, inclusion complexes, Nano suspensions, and lipid-based drug delivery systems. More recently, nanotechnology-based drug delivery systems**,** particularly dendrimers, have attracted considerable attention because of their ability to enhance the solubility and delivery of poorly water-soluble drugs. Among these nanocarriers, poly(amidoamine) (PAMAM) dendrimers possess unique characteristics such as a highly branched architecture, nanoscale size, internal cavities, and numerous surface functional groups that can encapsulate or complex hydrophobic drug molecules[26] .

The use of PAMAM dendrimers as carriers for Etoricoxib may significantly improve the drug's aqueous solubility, dissolution characteristics, and therapeutic effectiveness by enhancing its bioavailability. Therefore, understanding the physicochemical and pharmacological properties of Etoricoxib is essential for the rational design and development of nanocarrier-based drug delivery systems aimed at improving its clinical performance [27].

3. APPROACHES OF SOLUBILITY ENHANCEMENT:

Etoricoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, is classified as a Biopharmaceutics Classification System (BCS) Class II drug, meaning it exhibits low aqueous solubility but high membrane permeability. Because of its poor water solubility, the formulation of Etoricoxib presents significant challenges, particularly in oral drug delivery systems. As a result, considerable interest has developed in the application of nanotechnology-based drug delivery systems**,** including dendrimers, to overcome solubility-related limitations and improve drug dissolution and bioavailability [28].

Among various nanocarriers, poly (amidoamine) (PAMAM) dendrimers are highly effective polymeric nanocarriers composed of repeating amide and amine linkages arranged in a highly branched three-dimensional structure. The basic architecture of PAMAM dendrimers consists of a central core, repetitive branching units, and numerous terminal functional groups. This unique structural organization provides internal cavities capable of accommodating hydrophobic drug molecules while simultaneously offering external functional groups that allow interactions with drug molecules on the dendrimer surface. Such structural characteristics enable dendrimers to encapsulate or complex poorly soluble drugs, thereby improving their aqueous solubility and stability [29].

Encapsulation of drug molecules within the internal cavities of PAMAM dendrimers represents an effective approach to improving drug solubility. The hydrophobic interior regions of dendrimers can accommodate poorly soluble drug molecules, thereby increasing the apparent solubility of the drug in aqueous environments. In addition, encapsulation helps improve drug dispersion in aqueous media and reduces aggregation of hydrophobic molecules. Research studies indicate that several factors influence the degree of solubility enhancement, including the generation of the dendrimer, dendrimer concentration, structural characteristics, and physicochemical properties of the drug molecule**.**

Another important mechanism responsible for solubility enhancement involves the formation of hydrogen bonding and electrostatic interactions between drug molecules and the functional groups present on the surface of PAMAM dendrimers. Because PAMAM dendrimers possess multiple terminal amine or carboxyl functional groups, ionizable drugs can interact with these groups through electrostatic attraction or hydrogen bonding, which stabilizes the drug–dendrimer complex and improves drug solubilization in aqueous environments. Furthermore, the presence of numerous surface functional groups allows chemical modification or functionalization of dendrimers, thereby improving drug compatibility and enhancing solubility characteristics of the resulting complexes [30].

Surface modification and generation optimization of PAMAM dendrimers are also important factors for improving drug delivery performance while minimizing toxicity. Surface modification using hydrophilic polymers such as polyethylene glycol (PEG) or acetyl groups, as well as other biocompatible ligands, can improve water dispersibility, stability, and biocompatibility of dendrimer–drug complexes. Additionally, higher generations of PAMAM dendrimers possess larger internal cavities and a greater number of terminal functional groups, which increases drug loading capacity and enhances solubilisation efficiency. Consequently, PAMAM dendrimers represent promising nanocarriers for improving the solubility, dissolution rate, and delivery of poorly water-soluble drugs such as Etoricoxib [31].

4. DENDRIMERS IN DRUG DELIVERY:

Dendrimer is a term used to describe a class of macromolecules composed of highly branched polymeric structures that exist at the nanoscale and have gained considerable importance in the development of advanced drug delivery systems. These nanosized polymers possess well-defined architectures and controlled molecular weights, making them valuable carriers for pharmaceutical applications [32].

Dendrimers generally consist of three fundamental structural components:

a) A central core or initiator molecule,

b) Multiple layers of repeatedly branched units known as generations, and

c) Numerous terminal functional groups located on the dendrimer surface.

The presence of internal cavities within dendrimers allows drug molecules to be encapsulated, while the abundant surface functional groups enable interactions with drug molecules through various physicochemical mechanisms. These characteristics make dendrimers highly suitable for forming stable molecular complexes with a wide range of therapeutic agents. Because dendrimers possess a well-defined molecular size, controlled architecture, and a large number of functional surface groups, they are considered promising nanocarriers for improving the delivery and therapeutic efficacy of poorly soluble drugs.

Different approaches can be employed to create stable drug–dendrimer complexes, including encapsulation within internal cavities and chemical conjugation to surface functional groups. These strategies enable dendrimers to accommodate both hydrophobic and hydrophilic drugs.

Hydrophobic drugs may be incorporated into dendrimers through several mechanisms, including:

a) Hydrophobic interaction

b) Hydrogen bonding, and

c) Electrostatic interactions between the drug molecule and dendrimer structure.

Alternatively, drugs may also be attached to the dendrimer surface through different mechanisms such as:

a) Covalent (irreversible) bonding,

b) Non-covalent (reversible) binding, and

c) Modification of terminal functional groups on the dendrimer surface

PAMAM dendrimers have been widely investigated for their applications in nanomedicine and drug delivery due to their high biocompatibility and structural versatility. The nanoscale size and well-defined architecture of PAMAM dendrimers enable efficient transport of therapeutic agents across biological barriers and support controlled drug release. Additionally, dendrimers can be chemically modified with targeting ligands, imaging agents, or hydrophilic polymers to improve pharmacokinetic properties and enable site-specific drug delivery.

Dendrimers therefore represent an important class of nanocarriers in modern drug delivery systems. Their multifunctional architecture improves drug solubility, enhances permeability, facilitates targeted drug delivery, and allows controlled drug release profiles. Owing to these advantages, dendrimer-based drug delivery systems are being extensively investigated for the delivery of various therapeutic agents including anti-inflammatory, anticancer, antiviral, and antimicrobial drugs. Consequently, dendrimers are increasingly recognized as promising carriers for improving the delivery and therapeutic performance of poorly soluble drugs such as Etoricoxib [33].

5. PAMAM DENDRIMER:

PAMAM Dendrimer (poly (amidoamine) dendrimers) are highly branched, three-dimensional polymeric nanostructures composed of poly (amidoamine) chains containing amide and amine linkages. These dendrimers were first synthesized by Donald A. Tomalia and colleagues in 1985, introducing a new class of macromolecules known as dendritic polymers with potential applications in drug delivery systems. Due to their nanoscale size, well-defined architecture, and controlled molecular weight, PAMAM dendrimers have attracted considerable attention as promising nanocarriers for controlled drug delivery. Their structural uniformity and tunable surface functionality make them suitable candidates for improving the solubility and bioavailability of poorly soluble drugs.

A distinctive feature of PAMAM dendrimers is their generation-based architecture. Each generation represents an additional layer of branching units extending outward from the central core. As the dendrimer generation increases, the number of terminal functional groups on the surface also increases, resulting in greater surface area and larger internal cavities capable of accommodating drug molecules. These internal cavities can encapsulate hydrophobic drugs, while the surface functional groups such as amine, hydroxyl, or carboxyl groups allow drug molecules to interact with the dendrimer through hydrogen bonding, electrostatic interactions, and hydrophobic interactions. These properties contribute to improved aqueous solubility and enhanced stability of poorly soluble therapeutic agents.

PAMAM dendrimers therefore serve as effective nanocarriers or nanotransporters in drug delivery systems. Their nanoscale size and globular structure facilitate improved drug dispersion in aqueous media and enhance drug dissolution rates, ultimately increasing the bioavailability of therapeutic agents. Furthermore, the size and structural characteristics of PAMAM dendrimers allow them to cross biological barriers and interact efficiently with cellular membranes, which improves drug transport within biological systems.

Another advantage of PAMAM dendrimers is their ability to undergo surface modification. Functionalization with polymers, targeting ligands, or imaging agents can enhance biocompatibility, reduce toxicity, and enable targeted drug delivery to specific tissues or cells. Such modifications make PAMAM dendrimers useful carriers for a variety of therapeutic agents including anti-inflammatory, anticancer, and antiviral drugs.

Despite their promising properties, some limitations remain, including potential cytotoxicity associated with positively charged surface groups and challenges related to large-scale manufacturing. To overcome these limitations, researchers have explored surface modification techniques such as acetylation and polyethylene glycol (PEG) conjugation, which can improve the safety profile and reduce toxicity of PAMAM dendrimers. With ongoing advances in nanotechnology and polymer chemistry, PAMAM dendrimers are expected to play an important role in modern drug delivery systems, particularly for enhancing the solubility and therapeutic performance of poorly soluble drugs such as Etoricoxib [34].

6. MECHANISM OF DRUG SOLUBILIZATION BY PAMAM DENDRIMERS:

Poorly soluble drugs can be made less difficult to dissolve in water when they are solubilized with poly (amidoamine) (PAMAM), which is a type of dendrimer. Dendrimers are characterized by structural features such as central cores, branched generation structures, and many functional groups located on their surfaces (i.e., primary amines or hydroxyls). PAMAM dendrimers have an internal cavity structure that allows them to interact with drug molecules through multiple modes of action. This leads to an increase in the amount and rate of dissolution of these types of compounds in the aqueous environment when they are used in formulation applications .Research published on nanotechnology or drug delivery indicates that the interactions between dendrimers and poorly soluble therapeutic agents will be important for increasing their overall effectiveness or performance [35].

Dendrimers derived from poly (amidoamine) (commonly known as PAMAM) possess a branched structure with the ability to encapsulate and solubilize drugs. The branching characteristics of PAMAM dendrimers provide for mid-level hydrophobicity inside the core of the PAMAM dendrimer, allowing hydrophobic spaces to be formed that can store drug molecules .For example, a very poorly soluble drug such as Etoricoxib (an NSAID) when added to a PAMAM dendrimer solution can be encapsulated within the cavitary structure of the dendrimer through hydrophobic interactions between the drug and the dendrimer **.**Entrapment of poorly soluble drugs like Etoricoxib in PAMAM dendrimers results in greater apparent solubility than would otherwise be obtained without the dendrimer. Furthermore, it decreases the potential for drug aggregation and thereby increases the amount of drug that remains soluble.

The second major mechanism involves interaction of drug molecules with the surface functional groups of dendrimers via electrostatic forces and hydrogen bonding **.**Due to the large number of terminal groups present on PAMAM dendrimers, numerous interactions with drug molecules are possible through ionic attraction and hydrogen bonding **.**These interactions help stabilize the drug–dendrimer complex and improve dispersion of the drug in aqueous environments. The strength of these interactions is influenced by factors such as dendrimer generation, surface chemistry, pH of the solution, and physicochemical properties of the drug [36].

In addition to electrostatic interactions and encapsulation, other factors contributing to aqueous drug solubilization include adsorption and complexation. Hydrophobic and van der Waals interactions between drug molecules and the outer surface of dendrimers allow drugs to bind to the dendrimer surface. As the generation of dendrimers increases, the number of functional groups and internal cavities also increases, leading to greater drug loading capacity. Consequently, PAMAM dendrimers can significantly improve the solubility and dissolution profile of poorly soluble drugs through mechanisms such as encapsulation, electrostatic interaction, hydrogen bonding, and surface adsorption**.**Therefore, PAMAM dendrimers are considered effective nanocarriers for enhancing the solubility and pharmaceutical performance of poorly soluble drugs [37]**.**

7. APPLICATION OF PAMAM DENDRIMERS IN DRUG DELIVERY:

Dendritic nanocarriers that are extensively studied in pharmaceutical research include poly (amidoamine) (PAMAM) dendrimers**.** These materials were first synthesized in 1985 by Donald A. Tomalia and his colleagues, and they have attracted significant attention due to their highly branched architecture, nanometer-scale size, large number of surface functional groups, and internal cavities capable of encapsulating therapeutic agents**.** Because of these structural features, PAMAM dendrimers provide several advantages in pharmaceutical applications, including improved drug solubility, enhanced stability, and controlled drug delivery**,** making them promising carriers for a wide range of therapeutic compounds [38]**.**

7.1. SOLUBILITY ENHANCEMENT OF POORLY WATER-SOLUBLE DRUGS:

Low aqueous solubility is a major challenge in drug development because it can significantly limit drug absorption and therapeutic effectiveness. Dendrimers, particularly poly (amidoamine) (PAMAM) dendrimers, have emerged as promising nanocarriers for improving the solubility of hydrophobic drugs . These dendritic polymers enhance solubility by either encapsulating drug molecules within their internal cavities or by forming electrostatic interactions between drug molecules and functional groups present on the dendrimer surface**.** PAMAM dendrimers contain tertiary amine groups in their interior structure and terminal functional groups such as amine ($–NH_2$) or hydroxyl (–OH) groups on their surface, which facilitate the formation of host–guest complexes with drug molecules**.** As a result, the drug can be more effectively dispersed in aqueous media, increasing the amount of drug available for absorption in the body. Several studies have reported that PAMAM dendrimers significantly improve the solubility and bioavailability of poorly water-soluble drugs**,** including non-steroidal anti-inflammatory drugs (NSAIDs), anticancer agents, and antifungal drugs, thereby enhancing dissolution rates and therapeutic efficacy**.**

7.2. TARGETED DRUG DELIVERY:

PAMAM dendrimers can be engineered to develop targeted drug delivery systems by modifying the polymer structure and chemically conjugating various targeting ligands such as antibodies, peptides, folic acid, and sugars to the terminal functional groups present on the dendrimer surface**.** These targeting moieties enable the dendrimer–drug complex to selectively bind to specific receptors expressed on the surface of target cells**.** For example, folic acid–conjugated PAMAM dendrimers have been widely investigated for cancer therapy because many tumor cells overexpress folate receptors, allowing the dendrimer–drug complex to preferentially accumulate in malignant tissues**.** This receptor-mediated targeting strategy enhances the therapeutic efficacy of the drug by improving drug concentration at the site of disease while simultaneously reducing systemic toxicity and adverse effects associated with non-specific drug distribution**.**

7.3. CONTROLLED AND SUSTAINED DRUG RELEASE:

The unique branched architecture of poly (amidoamine) (PAMAM) dendrimers enables controlled delivery of therapeutic agents. Drug incorporation into PAMAM dendrimers can occur either through physical encapsulation within the internal cavities of the dendrimer or by covalent attachment of drug molecules to the terminal functional groups on the dendrimer surface. In covalent conjugation systems, the drug is released gradually through hydrolysis or enzymatic cleavage of the chemical bond under physiological conditions, resulting in a sustained release profile. Such controlled drug delivery systems help maintain therapeutic drug concentrations in the body for extended periods, reduce dosing frequency, and improve patient compliance while minimizing potential side effects associated with fluctuating drug levels.

7.4. GENE AND NUCLEIC ACID DELIVERY:

Researchers have extensively investigated poly (amidoamine) (PAMAM) dendrimers as non-viral vectors for gene delivery in gene therapy because of their unique structural and physicochemical properties. PAMAM dendrimers possess positively charged surface amino groups that can electrostatically interact with negatively charged nucleic acids such as DNA or RNA, forming stable complexes known as dendriplexes. These dendriplexes protect genetic material from enzymatic degradation during intracellular transport and facilitate efficient cellular uptake through mechanisms such as endocytosis. As a result, PAMAM dendrimers enhance the stability and delivery efficiency of therapeutic genes within cells. Several studies have demonstrated the potential application of PAMAM dendrimer-based gene delivery systems for the treatment of various diseases, including cancer, genetic disorders, and viral infections.

7.5. DRUG DELIVERY ACROSS BIOLOGICAL BARRIERS:

Poly (amidoamine) (PAMAM) dendrimers have been widely investigated for various drug delivery applications because of their nanoscale size, well-defined structure, and ability to be chemically modified. These nanocarriers can facilitate the transport of drugs across several biological barriers, including epithelial membranes, mucosal membranes, and even the blood–brain barrier, thereby improving drug permeability and absorption. PAMAM dendrimers typically possess nanometer-scale dimensions and their surface functional groups can be modified to alter surface charge, enhance biocompatibility, and improve drug delivery efficiency. Due to their small size and high degree of surface functionality, dendrimers can enhance tissue penetration and promote retention of drugs at the target site, improving therapeutic outcomes. Numerous studies have evaluated dendrimer-based formulations for different routes of administration, including ocular, transdermal, pulmonary, and nasal drug delivery systems, demonstrating their potential as versatile nanocarriers in modern pharmaceutical research.

7.6. ANTICANCER DRUG DELIVERY:

Cancer therapy is one of the most promising fields for dendrimer-based drug delivery systems. Conventional anticancer therapies often suffer from poor selectivity and significant systemic toxicity, which can limit their therapeutic effectiveness. Poly (amidoamine) (PAMAM) dendrimers can improve anticancer drug delivery because therapeutic agents can be either encapsulated within the internal cavities of the dendrimer or covalently conjugated to its surface functional groups, allowing more selective delivery to tumor tissues. In addition, the surface of PAMAM dendrimers can be modified with tumor-targeting ligands such as antibodies, peptides, or folic acid to enhance receptor-mediated targeting of cancer cells .The enhanced permeability and retention (EPR) effect in tumor tissues also promotes the accumulation of nanoscale drug carriers such as dendrimers at the tumor site . Several studies have investigated dendrimer-based delivery systems for anticancer drugs including methotrexate, doxorubicin, and paclitaxel, demonstrating improved drug targeting and therapeutic efficacy [39].

8. POTENTIAL APPLICATION OF ETORICOXIB:

Etoricoxib is a non-steroidal anti-inflammatory drug (NSAID) that selectively inhibits the enzyme cyclooxygenase-2 (COX-2), which is responsible for the synthesis of inflammatory mediators such as prostaglandins. It was developed as an alternative to conventional NSAIDs such as Ibuprofen and Naproxen, which inhibit both COX-1 and COX-2 and are often associated with gastrointestinal adverse effects. By selectively inhibiting COX-2, Etoricoxib reduces the production of prostaglandins involved in inflammation, pain, and fever. This reduction in prostaglandin synthesis leads to decreased inflammatory responses and contributes to its analgesic and antipyretic effects. Due to its selective mechanism and improved gastrointestinal safety profile compared with traditional NSAIDs, Etoricoxib has been widely studied and used in the management of inflammatory conditions such as osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and acute gouty arthritis [40].

8.1. ANKYLOSING SPONDYLITIS:

Ankylosing Spondylitis is a chronic inflammatory disease that primarily affects the axial skeleton, particularly the spine and the sacroiliac joints, leading to persistent pain, stiffness, and reduced spinal mobility. The inflammation mainly occurs in the joints between the vertebrae and the sacrum, which can gradually result in decreased flexibility and functional impairment of the spine. Etoricoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, is commonly used in the management of ankylosing spondylitis to relieve pain and reduce inflammation. By inhibiting COX-2–mediated prostaglandin synthesis, Etoricoxib helps decrease inflammatory responses and improves symptoms such as back pain and morning stiffness. Clinical studies have demonstrated that treatment with Etoricoxib and other COX-2 inhibitors can significantly improve physical function and reduce disease-related pain in patients with ankylosing spondylitis.

8.2. MANAGEMENT OF OSTEOARTHRITIS:

Osteoarthritis is a degenerative joint disorder characterized by the gradual breakdown of articular cartilage between bones, leading to joint pain, stiffness, reduced mobility, and the formation of bony outgrowths known as osteophytes. Local inflammation in the affected joints stimulates the production of prostaglandins, which contribute to pain and swelling. Etoricoxib is an effective treatment option for osteoarthritis because it selectively inhibits the cyclooxygenase-2 (COX-2) enzyme responsible for prostaglandin synthesis. By reducing prostaglandin production, Etoricoxib helps relieve pain, decrease inflammation, and improve joint function, enabling patients to maintain daily activities more comfortably. Compared with traditional non-steroidal anti-inflammatory drugs such as Ibuprofen and Naproxen, Etoricoxib selectively inhibits COX-2 without significantly affecting COX-1, which is associated with a lower incidence of gastrointestinal adverse effects. For optimal therapeutic benefit, Etoricoxib is generally administered once daily, which helps maintain consistent anti-inflammatory and analgesic effects.

8.3. TREATMENT OF RHEUMATOID ARTHRITIS:

Rheumatoid Arthritis is a chronic autoimmune inflammatory disorder that primarily affects synovial joints, leading to pain, swelling, stiffness, and progressive joint destruction. Inflammatory mediators such as prostaglandins play a major role in the development of pain and inflammation associated with this disease. Etoricoxib has been shown to reduce joint inflammation in rheumatoid arthritis by selectively inhibiting the cyclooxygenase-2 (COX-2) enzyme, thereby decreasing prostaglandin synthesis responsible for inflammatory responses. Through this mechanism, Etoricoxib provides effective analgesic and anti-inflammatory effects, which help reduce joint pain, swelling, and stiffness in patients with rheumatoid arthritis. Clinical studies have demonstrated that patients receiving Etoricoxib therapy experience significant improvement in pain relief and functional status compared with untreated patients, making it a useful therapeutic option in the symptomatic management of rheumatoid arthritis.

8.4. ACUTE PAIN MANAGEMENT:

Etoricoxib has been extensively studied for the management of moderate-to-severe acute pain, particularly postoperative pain following dental or orthopedic surgical procedures. Acute pain is often associated with tissue injury and inflammation, which stimulate the production of prostaglandins through the activity of the cyclooxygenase-2 (COX-2) enzyme. By selectively inhibiting COX-2, Etoricoxib reduces prostaglandin synthesis, thereby decreasing nociception and inflammatory responses associated with tissue damage. Clinical studies have demonstrated that EStoricoxib provides effective analgesia and reduces postoperative pain intensity in patients undergoing surgical procedures. In addition, Etoricoxib has a relatively long duration of action, allowing for convenient once-daily dosing, which enhances patient adherence and provides prolonged analgesic effects for pain management.

8.5. POTENTIAL ROLE IN TARGETED DRUG DELIVERY RESEARCH:

Etoricoxib has attracted increasing research interest in the development of advanced drug delivery systems aimed at improving its therapeutic performance. One of the major limitations of Etoricoxib is its poor aqueous solubility, which can restrict its dissolution rate and bioavailability after oral administration. To overcome this limitation, various nanocarrier-based delivery systems, including dendrimers, nanoparticles, and liposomes, are being investigated to enhance its solubility and improve drug targeting. Among these systems, dendrimers particularly poly (amidoamine) (PAMAM) dendrimers have shown considerable potential due to their well-defined nanostructure, high surface functionality, and ability to encapsulate or conjugate drug molecules. The incorporation of Etoricoxib into dendrimer-based systems may enhance its dissolution profile, bioavailability, and controlled release, thereby reducing systemic side effects and improving overall therapeutic efficacy [41].

9. METHODS FORPREPARATION OF DRUG-DENDRIMER COMPLEX:

The formation of drug–dendrimer complexes is a crucial step in the development of dendrimer-based drug delivery systems, particularly for enhancing the aqueous solubility of poorly soluble drugs such as Etoricoxib. Several preparation methods have been reported in pharmaceutical and nanotechnology literature to facilitate effective interaction between drugs and dendrimers. These interactions generally occur through non-covalent mechanisms such as hydrophobic interactions, hydrogen bonding, and electrostatic attraction between the drug molecules and the functional groups present on the dendrimer surface. The selection of an appropriate complexation method depends on several factors including the physicochemical properties of the drug, the generation of the dendrimer, and the desired characteristics of the final formulation.

One widely used technique for studying drug–dendrimer interactions is the equilibrium dialysis method. In this method, a mixture of the drug and dendrimer solution is placed inside a dialysis membrane and allowed to equilibrate with an external aqueous medium. Free drug molecules diffuse through the membrane while the dendrimer–drug complex remains inside the dialysis bag. After equilibrium is achieved, the distribution of the drug between the internal and external media can be analyzed to determine the degree of complex formation and solubilization efficiency [42].

Another commonly used preparation technique is the co-solvent method, in which the poorly soluble drug is first dissolved in a water-miscible organic solvent and then mixed with the dendrimer solution under continuous stirring. The drug solution is often added dropwise to the dendrimer solution to facilitate encapsulation within the internal cavities of the dendrimer and interaction with its surface functional groups. Subsequent removal of the organic solvent or dilution with water leads to the formation of the final drug–dendrimer complex. This method is particularly useful for drugs that require organic solvents for dissolution before complexation.

A further approach involves simple mixing or incubation methods, where the poorly soluble drug is directly added to an aqueous dendrimer solution and stirred or incubated for a specific period. During this process, the drug molecules become incorporated within the dendrimer structure through internal encapsulation and surface interactions. The resulting mixture is then filtered to remove unbound drug, producing the final drug–dendrimer complex. Due to its simplicity and minimal use of organic solvents, this method is frequently used in pharmaceutical research involving dendrimer-based nanocarrier systems [43].

10. CHARACTERIZATION TECHNIQUES:

The characterization of drug–dendrimer interactions is essential for evaluating the efficiency of dendritic nanocarriers in pharmaceutical drug delivery systems. Prior to their application in drug delivery, it is important to confirm that the drug molecule successfully binds to the dendrimer, as this indicates effective drug loading and helps researchers evaluate the physicochemical properties and stability of the drug–dendrimer complex**.** Among different dendritic polymers, poly(amidoamine) (PAMAM) dendrimers are one of the most extensively studied nanocarriers in pharmaceutical research due to their well-defined structure, high degree of surface functionality, and ability to encapsulate or conjugate drug molecules **.**During characterization studies, several parameters are commonly evaluated, including the size and morphology of the complex, the binding location between the drug and dendrimer, molecular interactions, and the presence of any unbound drug after complex formation.

One of the most widely used techniques for identifying chemical interactions between drugs and dendrimers is Fourier Transform Infrared Spectroscopy (FTIR). FTIR analysis detects vibrational changes in functional groups present in both the drug and the dendrimer. Shifts in characteristic absorption bands may indicate the formation of hydrogen bonding or other intermolecular interactions between the drug molecules and dendrimer surface groups **.**Nuclear Magnetic Resonance (NMR) spectroscopy is another important analytical technique that provides detailed structural information about molecular interactions and the environment of the drug molecules within the dendrimer structure [44].

In addition to spectroscopic methods, several physicochemical characterization techniques are used to evaluate dendrimer-based nanocarriers**.** Dynamic Light Scattering (DLS**)** is commonly employed to determine the particle size distribution of dendrimer complexes in solution, while zeta potential analysis measures surface charge and provides information about the stability of the nanocarrier system in aqueous dispersion. Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD) are frequently used to study the physical state and crystallinity of the drug after complex formation. These techniques help determine whether the drug remains crystalline or becomes amorphous when incorporated into the dendrimer matrix, which can significantly influence drug solubility and dissolution rate .Furthermore, imaging techniques such as Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are used to analyze the morphology and surface structure of dendrimer complexes. Collectively, these characterization methods provide valuable insights into the physicochemical properties of dendrimer-based drug delivery systems and help determine their potential to enhance the solubility and therapeutic performance of poorly water-soluble drugs such as Etoricoxib [45].

11. ADVANTAGES OF PAMAM DENDRIMER DRUG DELIVERY:

PAMAM dendrimers are among the most extensively studied nanocarriers in the field of drug delivery. Their highly branched three-dimensional architecture, nanoscale size, and the presence of multiple functional groups on their surface make PAMAM dendrimers particularly attractive for pharmaceutical applications. These structural characteristics allow PAMAM dendrimers to encapsulate or conjugate therapeutic agents efficiently, thereby improving drug solubility, stability, and bioavailability. Furthermore, the presence of numerous surface functional groups enables surface modification and targeted drug delivery, which enhances therapeutic efficacy and reduces systemic toxicity. Due to these advantageous physicochemical properties, PAMAM dendrimers have shown significant potential to outperform conventional drug delivery systems and are increasingly being explored for the delivery of poorly soluble drugs and targeted therapies.

11.1. WELL-DEFINED AND CONTROLLED STRUCTURE:

A major benefit of using PAMAM dendrimers as drug carriers arises from their precisely controlled molecular architecture. These macromolecules are synthesized through a stepwise and iterative process, which results in well-defined structures with specific characteristics such as size, shape, and molecular weight. This controlled synthesis produces highly monodisperse macromolecules, distinguishing dendrimers from many conventional polymeric carriers that often exhibit heterogeneous size distributions. The structural uniformity of PAMAM dendrimers contributes to reproducible drug loading, consistent drug release behavior, and predictable pharmacokinetic profiles. Consequently, dendrimers offer significant advantages as nanocarriers for drug delivery applications.

11.2. HIGH DRUG LOADING CAPACITY:

PAMAM dendrimers possess numerous surface functional groups and a unique three-dimensional architecture that includes internal cavities capable of accommodating therapeutic molecules. These structural features allow dendrimers to deliver drugs through different mechanisms. Drug molecules can be physically encapsulated within the internal voids of the dendrimer through non-covalent interactions such as hydrophobic interactions or hydrogen bonding, or they can be chemically conjugated to the terminal functional groups present on the dendrimer surface. As the dendrimer generation increases, the number of terminal functional groups also increases, resulting in a larger surface area and enhanced drug loading capacity. Therefore, higher-generation dendrimers generally exhibit greater capability for drug incorporation and delivery compared with lower-generation dendrimers.

11.3. IMPROVEMENT OF DRUG SOLUBILITY:

Many drugs exhibit poor aqueous solubility due to their chemical structure, which can limit their bioavailability and therapeutic effectiveness. PAMAM dendrimers have been widely investigated as solubility-enhancing nanocarriers for hydrophobic drugs. These dendrimers can improve drug solubility through various interactions such as hydrogen bonding, electrostatic interactions, and host–guest complex formation between the drug molecules and the dendrimer structure. In aqueous environments, PAMAM dendrimers possess a hydrophilic outer surface that helps maintain uniform dispersion in solution, while their internal cavities provide space for the encapsulation of poorly soluble or hydrophobic drug molecules. This dual structural characteristic enables PAMAM dendrimers to effectively enhance the solubility of hydrophobic drugs and improve their pharmaceutical performance.

11.4. TARGETED DRUG DELIVERY CAPABILITY:

The surface functional groups of PAMAM dendrimers can be easily modified, allowing the attachment of various targeting ligands such as antibodies, peptides, carbohydrates, and folic acid. These ligands enable dendrimer–drug complexes to recognize and bind selectively to specific receptors expressed on diseased or cancerous cells. Such targeted delivery systems improve the localization of therapeutic agents at the desired site of action, thereby increasing drug accumulation in diseased tissues while minimizing exposure to healthy cells. As a result, targeted dendrimer-based drug delivery can enhance therapeutic efficacy and reduce the likelihood of systemic side effects.

11.5. VERSATILITY IN DRUG DELIVERY APPLICATION:

Different forms of PAMAM dendrimers can be modified to support multiple routes of drug administration, including oral, ocular, transdermal, pulmonary, and intravenous delivery. Their versatile and highly tunable structure allows them to be engineered for specific biomedical applications. PAMAM dendrimers can simultaneously incorporate therapeutic drugs, targeting ligands, and imaging agents within a single nanostructure, resulting in multifunctional systems. Because of these properties, dendrimers are widely explored as advanced drug delivery platforms and have significant potential in the development of theranostic systems, which combine diagnostic and therapeutic functions within a single formulation.

11.6. PROTECTION OF DRUG MOLECULES:

By encapsulating or conjugating drugs within dendrimers, the therapeutic agents can remain stable during their transport through the bloodstream until they reach the intended site of action. Dendrimers protect drug molecules from premature degradation caused by enzymatic activity, hydrolysis, and environmental factors such as light and temperature. This protective capability enhances drug stability and improves the likelihood that the drug will reach the target tissue in its active and unaltered form, thereby increasing therapeutic efficacy and reducing drug loss during systemic circulation [46].

12. LIMITATIONS AND CHALLENGES:

PAMAM dendrimers are considered promising nanocarriers for drug delivery; however, further investigation is required before their widespread clinical application can be realized due to several associated limitations. The effectiveness of PAMAM dendrimers as drug delivery systems arises from their well-defined molecular architecture, nanoscale size, and versatile physicochemical properties. Despite these advantages, concerns remain regarding their potential toxicity, including cytotoxicity and neurotoxicity, as well as their unusual interactions with blood components that may influence coagulation. In addition, the complex synthesis process of dendrimers often leads to high manufacturing costs, which can limit large-scale production and clinical translation. Therefore, understanding these limitations is essential for the development of modified dendrimer systems or dendrimer-based composites with improved biocompatibility, reduced toxicity, and enhanced therapeutic performance in drug delivery applications [47].

12.1. CYTOTOXICITY ASSOCIATED WITH SURFACE CHARGE:

One of the major limitations associated with PAMAM dendrimers is their potential cytotoxicity, particularly for dendrimers containing terminal amine groups. The positively charged surface amine groups can strongly interact with negatively charged biological membranes, which may lead to membrane destabilization and cellular damage. The level of cytotoxicity is often influenced by the dendrimer generation and surface charge density. Higher-generation PAMAM dendrimers possess a greater number of terminal amine groups, resulting in stronger interactions with cell membranes and consequently an increased risk of cytotoxic effects. To reduce these adverse effects, several strategies have been developed to modify the dendrimer surface with neutral or biocompatible moieties such as polyethylene glycol (PEG), acetyl groups, or carbohydrates. These surface modifications mask the positive surface charge of the dendrimers, thereby improving their biocompatibility and reducing toxicity while maintaining their effectiveness as drug delivery carriers.

12.2. HEMOLYTIC TOXICITY:

Another important concern related to PAMAM dendrimers is their potential hemolytic activity when they come into contact with red blood cells. Positively charged dendrimers, particularly those with terminal amine groups, can interact with the negatively charged membranes of erythrocytes through electrostatic interactions. These interactions may disrupt the integrity of the cell membrane, resulting in membrane damage, rupture, and hemolysis. The extent of hemolytic toxicity is influenced by several factors including the dendrimer generation, concentration, and type of surface functional groups. Higher-generation dendrimers generally possess a greater number of surface amine groups and therefore exhibit stronger interactions with erythrocyte membranes, increasing the likelihood of hemolysis. However, surface modification of PAMAM dendrimers with neutral or biocompatible groups such as polyethylene glycol (PEG), acetyl groups, or hydroxyl groups has been shown to significantly reduce their hemolytic activity and improve their overall hemocompatibility.

12.3. NON-SPECIFIC BIODISTRIBUTION:

Although engineered dendrimers have the ability to deliver drugs with improved precision, unmodified PAMAM dendrimers may show non-specific biodistribution within the body. When administered through the intravenous route, PAMAM dendrimers can accumulate in organs such as the liver, kidneys, and spleen due to their interactions with plasma proteins and uptake by the reticuloendothelial system (RES). This unintended accumulation may lead to potential toxicity and can reduce the efficiency of targeted drug delivery. To overcome these limitations, researchers have explored various surface modification strategies such as conjugation with targeting ligands or hydrophilic polymers like polyethylene glycol (PEG). These modifications help improve circulation time, reduce nonspecific organ accumulation, and enhance the in vivo distribution and targeting efficiency of dendrimer-based drug delivery systems [48].

12.4. RAPID CLEARANCE AND BIOLOGICAL BARRIERS:

However, the application of dendrimer-based drug delivery systems is limited by their pharmacokinetic behavior in the body. Smaller dendrimers, particularly those below generation 3, are rapidly cleared from systemic circulation through renal filtration because of their small molecular size. As a result, these dendrimers may remain in circulation only for a short period of time, often being eliminated after passing through the kidneys. In contrast, higher-generation dendrimers possess larger molecular sizes, which can prolong their circulation time but may also reduce their ability to penetrate biological barriers and tissues effectively. Therefore, one of the major challenges in designing dendrimer-based drug delivery systems is achieving an optimal balance between dendrimer size, circulation time, and tissue penetration to ensure efficient therapeutic delivery [49].

12.5. COMPLEXITY OF SYNTHESIS AND PRODUCTION COST:

PAMAM dendrimers are synthesized through a series of stepwise reactions that allow the controlled growth of highly branched macromolecules. Each synthetic step must be carefully carried out to ensure the formation of uniform and well-defined dendrimer structures. As the generation number increases (e.g., Generation 1, Generation 2, and higher), the synthesis becomes progressively more complex, requiring multiple reaction and purification steps. Consequently, the production of higher-generation PAMAM dendrimers becomes more time-consuming and expensive, particularly when large-scale manufacturing is considered. In addition, purification of dendrimers is essential to remove incomplete structures, side products, and residual reagents formed during synthesis. Proper purification ensures the reproducibility, safety, and quality of PAMAM dendrimers intended for pharmaceutical and biomedical applications.

12.6. LIMITED CLINICAL TRANSLATION:

Despite extensive research in the field of nanomedicine, only a limited number of dendrimer-based drug delivery systems have progressed to clinical application. This limitation is mainly associated with concerns related to potential toxicity, complex regulatory requirements, and the need for extensive safety and pharmacokinetic evaluations before approval for human use. Additionally, variations in dendrimer size, surface charge, and functional groups may influence their biological interactions and safety profiles, making comprehensive toxicity assessment essential. Therefore, further research aimed at improving the biocompatibility of dendrimers, optimizing their structural design, and conducting long-term in vivo toxicity studies is necessary to facilitate the successful clinical translation of dendrimer-based nanocarrier systems [50].

13. FUTURE PERSPECTIVES:

PAMAM dendrimers have demonstrated considerable potential as nanocarriers for improving the solubility of poorly water-soluble drugs such as etoricoxib. Advances in nanotechnology and pharmaceutical sciences have encouraged the exploration of dendrimer-based systems in drug formulation development. However, extensive studies are still required to evaluate the efficiency of PAMAM dendrimers as drug delivery systems and to optimize their ability to enhance the solubility of poorly soluble drugs like etoricoxib. Research in this area may significantly improve the pharmacokinetic and pharmacodynamic properties of many therapeutic agents. Furthermore, future investigations may focus on surface modification and functionalization of PAMAM dendrimers to design safer and more effective drug delivery systems. Surface engineering using polymers, peptides, or other targeting ligands may enable selective delivery of etoricoxib to inflamed tissues, thereby improving therapeutic efficacy and reducing systemic adverse effects [51].

In addition, further in vivo and clinical studies are necessary to obtain a more comprehensive understanding of the pharmacokinetics, biodistribution, and long-term safety of dendrimer-based drug delivery systems. Although experimental studies have demonstrated improvements in solubility and drug-loading capacity with PAMAM dendrimers, rigorous evaluation of toxicity, metabolism, and elimination pathways is essential before clinical translation. Future research should also focus on developing scalable and cost-effective synthetic approaches for producing dendrimer formulations in large quantities to meet pharmaceutical manufacturing requirements [52].

14. CONCLUSION:

Research has demonstrated that poly (amidoamine) (PAMAM) dendrimers are among the most promising nanocarriers for improving the solubility and bioavailability of poorly water-soluble drugs such as etoricoxib. PAMAM dendrimers possess a unique molecular architecture characterized by a highly branched three-dimensional structure with internal cavities and numerous terminal functional groups, particularly primary amine groups on their surface. This distinctive structure enables the encapsulation or interaction of drug molecules within the internal cavities or through surface functional groups, thereby enhancing drug solubility, dissolution rate, and bioavailability. Owing to these properties, PAMAM dendrimers have become an important focus in pharmaceutical nanotechnology research aimed at overcoming the solubility limitations of Biopharmaceutics Classification System (BCS) Class II drugs, which are characterized by low solubility but high permeability [53].

Despite their advantages, several challenges remain associated with the application of PAMAM dendrimers as drug delivery systems. These challenges include potential cytotoxicity related to surface amine groups, the complexity and cost associated with dendrimer synthesis, and regulatory considerations for clinical translation. Consequently, current research is largely directed toward surface modification, functionalization, and formulation strategies to enhance biocompatibility and safety. With continued advancements in nanotechnology and pharmaceutical sciences, PAMAM dendrimers are expected to play an important role in the development of advanced drug delivery systems capable of improving the therapeutic efficacy of poorly soluble drugs such as etoricoxib [54].

REFERENCES:

1. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: Importance and enhancement techniques. ISRN Pharmaceutics. 2012; 2012:195727.
2. Kalepu S, Nekkanti V. Insoluble drug delivery strategies: Review of recent advances and business prospects. Acta Pharm Sin B. 2015; 5(5):442–453.
3. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995; 12(3):413–420.
4. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poorly water-soluble drugs. Drug Discov Today. 2007; 12(23–24):1068–1075.
5. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Methods. 2000; 44(1):235–249.
6. Mohanty C, Sahoo SK. The in vitro stability and in vivo pharmacokinetics of curcumin prepared as an aqueous nanoparticulate formulation. Biomaterials. 2010; 31(25):6597–6611.
7. Torchilin VP. Multifunctional nanocarriers. Adv Drug Deliv Rev. 2012; 64(Suppl):302–315.
8. Tomalia DA, Baker H, Dewald J, Hall M, Kallos G, Martin S, et al. A new class of polymers: Starburst-dendritic macromolecules. Polym J. 1985; 17(1):117–132.
9. Svenson S, Tomalia DA. Dendrimers in biomedical applications—reflections on the field. Adv Drug Deliv Rev. 2005; 57(15):2106–2129.
10. Chauhan AS. Dendrimers for drug delivery. Molecules. 2018; 23(4):938.

11. Kesharwani P, Jain K, Jain NK. Dendrimer as nanocarrier for drug delivery. Prog Polym Sci. 2014; 39(2):268–307.
12. Riendeau D, Percival MD, Brideau C, et al. Characterization of etoricoxib, a potent and selective COX-2 inhibitor. J Pharmacol Exp Ther. 2001; 296(2):558–566.
13. Merck & Co. Arcoxia (etoricoxib) prescribing information. Whitehouse Station (NJ): Merck & Co.; 2023.
14. Patel RN, Patel MM. Enhancement of dissolution rate of etoricoxib by solid dispersion technique. Int J Pharm Pharm Sci. 2012; 4(Suppl 4):440–443.
15. Kawtikwar PS, Sakarkar DM. Solubility enhancement of poorly soluble drugs by novel drug delivery approaches. Int J PharmTech Res. 2011; 3(1):249–255.
16. Tomalia DA, Reyna LA, Svenson S. Dendrimers as multipurpose nanodevices for oncology drug delivery and diagnostic imaging. Biochem Soc Trans. 2007; 35(1):61–67.
17. Menjoge AR, Kannan RM, Tomalia DA. Dendrimer-based drug and imaging conjugates: Design considerations for nanomedical applications. Drug Discov Today. 2010; 15(5–6):171–185.
18. Gupta U, Jain NK. Dendrimers as potential drug carriers. J Pharm Pharmacol. 2010; 62(6):699–714.
19. Mintzer MA, Grinstaff MW. Biomedical applications of dendrimers: A tutorial. Chem Soc Rev. 2011; 40(1):173–190.
20. Porat D, Dukhno O, Partook-Maccabi M, Vainer E, Cvijić S, Dahan A. Selective COX-2 inhibitors after bariatric surgery: Celecoxib, etoricoxib and etodolac solubility and pharmacokinetics. Int J Pharm. 2023; 645:123347.
21. National Center for Biotechnology Information. PubChem compound summary for etoricoxib (CID: 123619). Bethesda (MD): NCBI; 2024.
22. AlKhalidi MM, Jawad FJ. Enhancement of aqueous solubility and dissolution rate of etoricoxib by solid dispersion technique. Iraqi J Pharm Sci. 2019; 29(1):76–87.
23. Patel RN, Manavi B, Patel S. Modification of physical and chemical properties of BCS class II drug etoricoxib. Int J Pharm Pharm Sci. 2012; 4(Suppl 4):403–406.
24. Rodrigues AD. Impact of cytochrome P450 enzymes on the metabolism of selective COX-2 inhibitors. Drug Metab Rev. 2005; 37(3):541–569.
25. Shadrack DM, Swai HS, Munissi JJE, Mubofu EB, Nyandoro SS. Polyamidoamine dendrimers for enhanced solubility of small molecules and site-specific delivery. Molecules. 2018; 23(6):1419.
26. Gautam SP, Gupta AK, Wani SUD, Malviya N, Gautam T, Sharma AK. PAMAM dendrimers mediated solubility enhancement of poorly soluble drugs: A concise review. Int J Pharm Drug Anal. 2015; 3(4):105–110.
27. Kulhari H, Pooja D, Prajapati SK, Chauhan AS. Performance evaluation of PAMAM dendrimer-based simvastatin formulations. Int J Pharm. 2011; 405(1–2):203–209.
28. Devarakonda B, Otto DP, Judefeind A, Hill RA, de Villiers MM. Effect of pH on the solubility and release of furosemide from polyamidoamine dendrimer complexes. Int J Pharm. 2007; 345(1–2):142–153.
29. Gupta U, Agashe HB, Asthana A, Jain NK. Dendrimers: Novel polymeric nanoarchitectures for solubility enhancement. Biomacromolecules. 2006; 7(3):649–658.
30. Majoros IJ, Myc A, Thomas T, Mehta CB, Baker JR Jr. PAMAM dendrimer-based multifunctional conjugate for cancer therapy: Synthesis and characterization. J Med Chem. 2005; 48(19):5892–5899.
31. Patri AK, Kukowska-Latallo JF, Baker JR Jr. Targeted drug delivery with dendrimers. Adv Drug Deliv Rev. 2005; 57(15):2203–2214.
32. Kukowska-Latallo JF, Bielinska AU, Johnson J, Spindler R, Tomalia DA, Baker JR Jr. Efficient transfer of genetic material into mammalian cells using PAMAM dendrimers. Proc Natl Acad Sci USA. 1996; 93(10):4897–4902.

33. Mintzer MA, Simanek EE. Nonviral vectors for gene delivery. Chem Rev. 2009; 109(2):259–302.
34. Svenson S, Tomalia DA. Dendrimers in biomedical applications. Adv Drug Deliv Rev. 2012; 64(2):102–115.
35. Kesharwani P, Jain NK. Dendrimer nanocarriers in drug delivery systems. Prog Polym Sci. 2014; 39(2):268–307.
36. Chauhan AS. Applications of dendrimers in drug delivery and therapeutics. Molecules. 2018; 23(4):938.
37. Tomalia DA. Birth of a new macromolecular architecture: Dendrimers as quantized building blocks. Prog Polym Sci. 2005; 30(3–4):294–324.
38. Duncan R, Izzo L. Dendrimer biocompatibility and toxicity. Adv Drug Deliv Rev. 2005; 57(15):2215–2237.
39. Esfand R, Tomalia DA. Poly(amidoamine) dendrimers: From biomimicry to drug delivery. Drug Discov Today. 2001; 6(8):427–436.
40. Svenson S. Dendrimers as versatile platform in drug delivery. Eur J Pharm Biopharm. 2009; 71(3):445–462.
41. Jain NK, Gupta U. Application of dendrimers in drug delivery and targeting. Int J Pharm. 2008; 346(1–2):1–13.
42. Patri AK, Majoros IJ, Baker JR Jr. Dendritic polymer macromolecular carriers for drug delivery. Curr Opin Chem Biol. 2002; 6(4):466–471.
43. Lee CC, MacKay JA, Frechet JMJ, Szoka FC. Designing dendrimers for biological applications. Nat Biotechnol. 2005; 23(12):1517–1526.
44. Tomalia DA, Naylor AM, Goddard WA. Starburst dendrimers: Molecular-level control of size, shape and functionality. Angew Chem Int Ed Engl. 1990; 29(2):138–175.
45. Caminade AM, Turrin CO. Dendrimers for drug delivery. J Mater Chem B. 2014; 2:4055–4066.
46. Gillies ER, Fréchet JMJ. Dendrimers and dendritic polymers in drug delivery. Drug Discov Today. 2005; 10(1):35–43.
47. Tomalia DA, Christensen JB, Boas U. Dendrimers, dendrons and dendritic polymers: Discovery, applications and the future. Cambridge: Cambridge University Press; 2012.
48. Svenson S. Clinical translation of dendrimer nanomedicine. Adv Drug Deliv Rev. 2012; 64:102–115.
49. Gupta U, Jain NK. Dendrimers in drug delivery: Progress and challenges. Drug Discovery Today. 2010; 15(17–18):717–726.
50. Kulhari H, Prajapati SK, Chauhan AS. Dendrimer-based drug delivery systems: From bench to clinic. J Pharm Pharmacol. 2016; 68(6):725–739.
51. Braun J, Sieper J. Ankylosing spondylitis. **Lancet.** 2007; 369(9570):1379-1390.
52. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet*. 2019; 393(10182):1745-1759.
53. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016; 388(10055):2023-2038.
54. Sinatra R. Causes and consequences of inadequate management of acute pain. **Pain Med.** 2010; 11(12):1859–1871.