

Literature Review



## The Dendrimers as Drug Delivery Platforms of the Mechanisms, Benefits, and Use in Anti-Pain: Systematic Literature Review

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### ABSTRACT

**Background:** Efforts to reduce the side effects of long-term NSAID use have prompted exploration of transdermal drug delivery, which offers advantages such as avoiding first-pass metabolism, reducing pain, allowing sustained drug release, and improving patient compliance. Dendrimers, specifically polyamidoamine (PAMAM), are attracting attention for their potential in drug delivery. PAMAM has a three-dimensional structure of monodisperses with high amino group density and internal voids suitable for drug encapsulation.

**Methods:** This research method uses the literature review method which begins with the collection of journals to be reviewed. The article search was conducted on the Pubmed database. Researchers searched with the keyword dendrimer. The two main synthesis methods are convergent and divergent dendrimers.

**Results:** : Drug molecules can be trapped in dendrimers through hydrogen, hydrophobic, or electrostatic bonds. The advantages of dendrimers include improved solubility, permeability, and targeted drug delivery, while the disadvantages are high cost, toxicity and aggregation. This system has been used in several pain medications.

**Conclusions:** Dendrimers are macrostructures with unique characteristics such as nanoscopic size, multifunctional surface, and high branching, making them ideal as drug delivery systems. Ketoprofen with PAMAM-type dendrimers showed that PAMAM dendrimers could significantly increase the accumulative amount of permeation of both drugs after 24 hours, compared with the drug suspension without PAMAM dendrimers. Dendrimers are multi-branched monodisperse macrostructures, derived from Greek.

**Keywords:** *Dendrimers, drug, Anti-Pain, Benefits*

## INTRODUCTION

Pain is often referred to as a reminder to protect the body from further tissue damage as it indicates that the body is experiencing tissue damage, inflammation, or more severe abnormalities such as nervous system dysfunction. Often, pain causes discomfort such as stabbing, burning, and shock, which interferes with the quality of life of the patient or person experiencing pain. Analgesics are a type of drug that is utilized to reduce or eliminate the sensation of pain without disturbing consciousness. They are commonly used to relieve pain, for example, when experiencing a headache or toothache. Some of the drugs that we often consume when we feel uncomfortable usually contain analgesics or pain relievers [1].

A drug delivery system is a mechanism used to deliver therapeutic substances or drugs that have been clinically and pre-clinically tested in the treating wardoa disease. Drug delivery can be done through various routes, where the most common methods involve oral intake or injection into a blood vessel [2]. Technological technological advancements have resulted in various drug carriers in targeted delivery systems, such as liposomes, micelles, nanoparticles, dendrimers, etc. These drug delivery systems must meet ideal standards, including that they are non-toxic, biocompatible, do not elicit an immune response, can be naturally degraded, and can avoid recognition by immune mechanisms in the body [3].

Efforts to reduce the side effects of long-term use of NSAIDs have led to the exploration of alternative administration

methods, such as transdermal drug delivery systems. Transdermal delivery offers advantages over oral and injectable administration, including avoiding first-pass metabolism, minimizing pain, allowing sustained drug release, and improving patient compliance. However, there have been studies on the transdermal delivery of NSAIDs. Dendrimers, hyperformed macromolecules, monodispersed, three-dimensional, have attracted attention for their potential in drug delivery. Polyamidoamine (PAMAM), a widely researched dendrimer with an ellipsoidal or spheroidal shape, stands out for its high amino group density and empty internal cavity suitable for drug encapsulation [4].

## METHODS

This research method uses the literature review method which begins with the collection of journals to be reviewed. The article search was conducted on the Pubmed database. Researchers searched with the keyword dendrimer. Next, the journal was reviewed for the title, abstract, and discussion results. Then, the remaining articles were selected according to the criteria, namely, discussing clearly and specifically about the dendrimer. Based on these criteria, there were seven articles, and a literature review was conducted.

## RESULTS

Since first reported by Fritz Vögtle in 1978, research on dendrimers has progressed rapidly in the past four decades, involving both synthesis and applications. The unique characteristics of the dendrimer structure, such as nanoscopic size, multifunctional surface, high branching, and extensive

interior, make it an ideal drug delivery system. The word dendrimer originates from the Greek "dendron," meaning tree or branch. In 1978, Buhleir and his team successfully synthesized and reported the first "cascade" and "non-slippery chain-like" molecules with molecular cavity topology, which became known as the early form of dendritic polymers. From 1979 to 1985, Donald A. Tomalia and the team at Dow Laboratories made breakthroughs in dendrimer development. They created polymers with a hollow core in the center and tendrils branching outward, towards each other, in a predictable manner, which Tomalia later called dendrimers. To date, more than 100 dendritic structures have been reported, including the most common dendritic families such as PolyAmidoamine (PAMAM) dendrimers, polypropylene (PPI) dendrimers, and polyamide, polyether, polyester, and phosphorus-based dendrimers. All these advances have promoted the growth of dendrimers and their applications in chemistry, materials, and biological and medical sciences [5].

In the pharmaceutical field, dendrimers are applied for drug delivery, drug solubility enhancers, cell delivery, and nano-drugs they can be applied to photodynamic therapy and gene transfer as drug delivery dendrimer works by encapsulation. Several types of dendrimers have been produced and applied including PolyAmidoamine (PAMAM) dendrimers, PolyPropylene Imine (PPI) dendrimers and PolyAmidoamine-Organosilicon. Dendrimer synthesis generally involves two methods known as convergent and divergent approaches. The convergent approach starts with a covalent reaction between one and the same monomer. This process is repeated to form layers that become the inner and outer parts

of the dendrimer. Once the layers are homogeneously formed, the core of the dendrimer is naturally formed.

On the other hand, the divergent approach starts with the formation of the divergent synthesis of dendrimers starts with the formation of a multifunctional core; then, by Michael's reaction, it is reacted with dendritic monomers, which are active functional groups. Each stage of the synthesis is carried out meticulously to avoid short branches. The degree of imperfection (low purity) may result in unsymmetrical dendrimer function and shape [6].

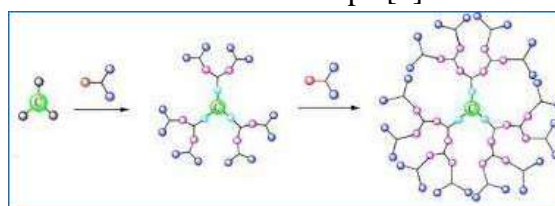


Figure 1. Divergent Synthesis

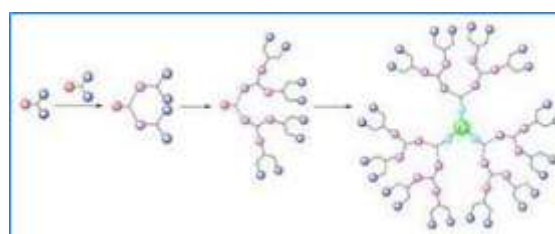


Figure 2. Convergent Synthesis

**Table 1. The following is a table of the types of dendrimer drugs along with their active ingredients and methods and results**

Active Ingredients	Dendrimer Type	Methods & Results
Meloxicam	Poly Dendrimer Amidoamine (PAMAM)	The dendrimer patch showed satisfactory characteristics. PAMAM dendrimer significantly improved (p<0.5) the permeation of MLX. A maximum



Active Ingredients	Dendrimer Type	Methods & Results
		drug release of 85.7% was achieved in 24 hours. Dendrimers may enhance the release of MLX by increasing its solubility and permeation through the membrane [7].
Ketorolac	Poly Dendrimer Amidoamine (PAMAM)	Optimized Dendrimer formulation resulted in significantly improved solubility of CTCs [8].
Ketoprofen	Poly Dendrimer Amidoamine (PAMAM)	In vitro permeation studies with rat skin showed that PAMAM dendrimers could significantly increase the accumulative amount of permeation of both drugs after 24 hours, compared with drug suspensions without PAMAM dendrimers [9].
Ibuprofen	Poly Dendrimer Amidoamine (PAMAM)	The results of this study show that the solubility properties of dendritic structures can increase as the core size and dendritic structure properties of dendrimers

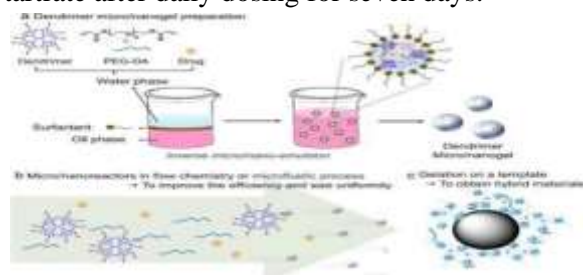
  

Active Ingredients	Dendrimer Type	Methods & Results
Flurbiprofen	Poly Dendrimer Amidoamine (PAMAM)	change [9]. Dendrimers interact with hydrophobic FB molecules to bring them to an ionized state, increasing state solubility in water [10].
Indomethacin	Polypropylene Imine (PPI) Dendrimer	PPI dendrimers can increase the solubility of indomethacin drugs. The maximum solubility increase in the case of IND was found at pH 7.4, 10.0, and pH 4.0 in its intrinsic solubility [11].
Piroxicam	Poly Dendrimer Amidoamine (PAMAM)	The optimal formulation contained 0.2% b/v PAMAM dendrimer at pH 7.4, which significantly increased PXM solubility [12].

## DISCUSSION

Dendrimer hydrogels (DH) have shown promising structural characteristics for localized drug delivery. All reactants are initially soluble in water and then converted into micro/nanodroplets in the continuous organic phase with the help of surfactants. The gelling reaction between dendrimer and PEG-DA occurs inside the micro/nanodroplets. By changing the preparation parameters, researchers could create micro and nano gel particles of varying sizes, ranging from a few micrometers to hundreds of nanometers. For the resulting dendrimer

microgels (3-5  $\mu\text{m}$ ), researchers adjusted the parameters to create dendrimer nanogels and tested them for topical drug delivery in antiglaucoma treatment. The results showed that dendrimer nanogels maximize the utilization of structural characteristics of existing dendrimer and hydrogel ocular drug delivery systems, with consideration of cellular compatibility, degradability, drug release kinetics, corneal permeability, and effectiveness of sustained intraocular pressure reduction. The intraocular pressure reduction achieved by nanogels containing brimonidine tartrate was fourfold more significant than that of free brimonidine tartrate after daily dosing for seven days.



**Figure 3. Preparation of micro dendrimer**

Micro dendrimers/nanogels combine the features of dendrimers, hydrogels, and micro/nanoparticles [5].

### Creation and Evaluation Test

Dendrimer generation is generally made by divergent or convergent synthesis.

The divergent synthesis of dendrimers starts with the formation of a multifunctional core, then by Michael reaction is reacted with dendritic monomers which are active functional groups. Each step of the synthesis is performed flawlessly to avoid the formation of short branches. Imperfections (low purity) result in functional and shape asymmetries. The divergent method approach successfully produces large quantities of dendrimers [6].

The convergent synthesis of dendrimers starts with a covalent reaction between the same monomer. The same reaction is then repeated to form layers which are the inner and outer shells. After the skin is homogeneously formed, the core

is automatically formed. This method is only suitable for the production of low-generation dendrimers [6].

### Identification and Characterization Test

With a complex structure, the characterization and analysis of dendrimers determine the molecular size, as well as several other analyses such as structure and shape. Several kinds of spectrometric methods can be used to characterize dendrimers, namely chromatography to determine the molecular weight and purity of the product such as liquid chromatography (LC), High-Performance Liquid Chromatography (HPLC), Gel Permeation Chromatography (GPC), Nuclear Magnetic Resonance (NMR) to determine the structure such as one dimensional (1D NMR), multidimensional NMR, diffusion NMR, dynamic NMR, other spectrometry such as mass spectrometry, MALDI and ESI, x-ray, small angle scattering, microscopy to determine the shape of the surface of the structure formed such as scanning probe microscopy, Transmission Electron Microscopy (TEM) [6]

### Stability Test

The stability of dendrimer preparations must be evaluated to ensure that they can last for a long time and do not degrade [7].

### Organoleptic Test

Tests were conducted to determine smoothness, color and thickness. Thickness was measured at five different locations using a screw screen, and the average thickness was determined. Ten patches from each batch were weighed individually, and the average weight was determined [7].

### Folding Resistance Test

This is done to determine the strength of the patch and to check the efficiency of the plasticizer. The way to determine this is by folding the patch many times in the same place until it breaks. The number of times the patch

can be folded in the same place without breaking or cracking, the folding resistance value can be known [7].

#### Drug Content Uniformity Test

A drug content uniformity test was performed on three patches. Each patch was soaked and dissolved in 50 ml of methanol, and the solution was filtered to remove the undissolved residue. Aliquots were prepared and measured spectrophotometrically for drug content at 365 nm wavelength [7].

#### In vitro Release Test

This test was performed to evaluate the extent to which a drug formulation releases its active substance from the delivery system. It was performed using a specially designed glass diffusion cell. The test was performed by pre-soaking a cellophane dialysis membrane for 24 hours in phosphate buffer pH 7.5. This membrane was stretched around one end of the diffusion cell. The working surface area of the membrane was 2.5 cm<sup>2</sup>.

The tube (donor compartment) is immersed in a beaker containing phosphate buffer pH 7.5 (receptor compartment receptor) so that the membrane touches the receptor medium. Weighed transdermal patches (1 cm<sup>2</sup>) were placed on the plastic dialysis membrane. The receptor medium was maintained at  $37 \pm 0.5^{\circ}\text{C}$  and stirred at 50 rpm on a magnetic stirring hot plate. Aliquots (5 ml) of samples were withdrawn from the receptor media at predetermined intervals and replaced with an equal volume of fresh buffer to maintain sink conditions. Samples were analyzed spectrophotometrically at 365 nm wavelength and drug release was calculated [7].

The advantages and disadvantages of dendrimers are improved drug solubility, increased permeability, and targeted drug delivery, while the disadvantages are high production costs, toxicity, and the occurrence of aggregation and agglomeration.

## CONCLUSIONS

Dendrimers are monodisperse macrostructures with many branches. The word dendrimer is of Greek origin. There are two standard methods of dendrimer synthesis: convergent and divergent dendrimers. The mechanism of dendrimers, is that drug molecules can be trapped in the core through hydrogen bonds, hydrophobic bonds, or electrostatic interactions. The advantages of dendrimer drug delivery systems are improved solubility, increased permeability and targeted drug delivery. While the disadvantages are high production costs, toxicity, aggregation and agglomeration, several pain medications have been made with dendrimer delivery systems.

## SUGGESTIONS

- a. Enhanced Training Programs: Develop comprehensive training programs for community nurses, focusing on insulin therapy management, patient education, and psychosocial support.
- b. Collaborative Care Models: Implement and evaluate collaborative care models that integrate community health nurses with primary care teams.
- c. Patient-Centered Approaches: Promote patient-centered approaches in diabetes care that emphasize individualized treatment plans and psychosocial support.
- d. Policy Support: Advocate for policies that recognize and support the expanded role of community health nurses in diabetes management.
- e. Arrange the distribution flow or mechanism efficiently so that drugs do not have dead stock [13].

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