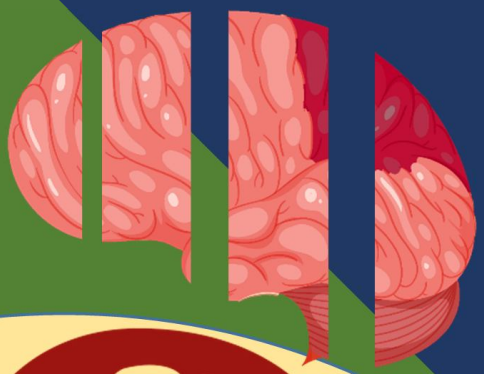
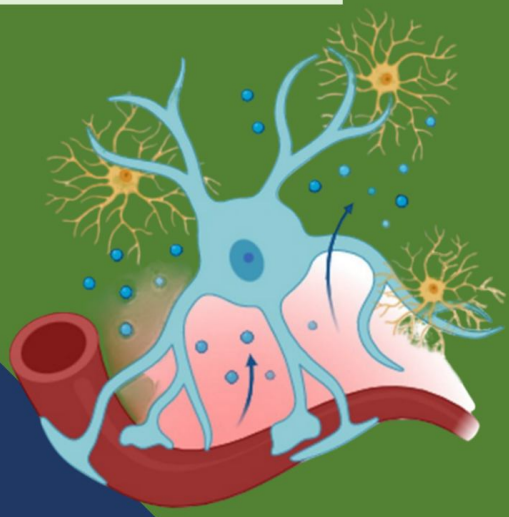
Advance Drug Deliveries for Alzheimer's Disease





Dr. Vaseem A. Ansari
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Advance Drug Deliveries for Alzheimer's Disease

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Advance Drug Deliveries for Alzheimer's Disease

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Preface

Welcome to the pages of **"Advance Drug Deliveries for Alzheimer's Disease."** This book is a journey into the ever-evolving world of Alzheimer's disease treatment, where innovative drug delivery systems play a pivotal role in our quest for more effective therapies. We commence our exploration by delving into the core concepts of Alzheimer's disease. From the intricate pathophysiology to the real-world impact on individuals and their families, we lay the foundation for comprehending the complexities of this condition. Alzheimer's disease presents unique challenges. Current treatments offer symptomatic relief, but a definitive cure remains elusive. We dissect these challenges, emphasizing the pressing need for advanced drug delivery systems to revolutionize treatment. The heart of this book lies in the exploration of cutting-edge drug delivery technologies. From nanoparticles and liposomes to sophisticated nanotechnological interventions, we unearth a realm of promise. These innovations aim to enhance drug targeting, improve bioavailability, and minimize adverse effects, offering a glimmer of hope for more effective Alzheimer's disease treatments. The future of Alzheimer's disease treatment is personalized. We explore the potential for tailored therapies and personalized medicine within the sphere of drug deliveries, recognizing the unique nature of each patient's journey with Alzheimer's. Throughout these pages, we underscore the critical role of research and collaborative efforts in advancing Alzheimer's disease drug delivery solutions. The synergy between academia, industry, and healthcare professionals is indispensable in propelling progress. As we conclude this book, we cast our gaze toward the future of Alzheimer's disease drug deliveries. From emerging technologies to ethical and regulatory considerations, we aim to provide a comprehensive view of what lies ahead. "Advance Drug Deliveries for Alzheimer's Disease" is a collective endeavor. It brings together the insights, expertise, and dedication of numerous researchers, scientists, and healthcare professionals. As editors and contributors, our hope is that this book serves as a catalyst, sparking further research, fostering new collaborations, and ultimately leading to more effective, targeted, and personalized solutions for Alzheimer's disease.

Authors

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Ms. Aditya Singh

Acknowledgement

Writing a book on **Advanced Drug Deliveries for Alzheimer's Disease** has been a challenging yet immensely rewarding endeavor. I would like to express my sincere gratitude toward Hon. Chancellor, Prof. Syed Waseem Akhtar, Integral University and Vice-Chancellor, Prof. Javed Musarrat, Integral University for providing research environment and all necessary facility for conducting research.

First and foremost, I extend my deepest appreciation to the researchers, scientists, and experts in the field of Alzheimer's disease and drug delivery systems. Your tireless dedication to advancing our understanding of this complex condition and developing innovative drug delivery solutions has been the foundation upon which this book is built.

I would also like to thank my colleagues, mentors, and academic advisors for their invaluable guidance and support throughout the process of researching and writing this book. Your insights and expertise have played a crucial role in shaping the content and ensuring its quality.

To the patients and families affected by Alzheimer's disease, I offer my heartfelt thanks for sharing your stories and experiences. Your resilience and courage in the face of this challenging condition have been a constant source of inspiration and a reminder of the importance of finding effective drug delivery solutions.

I extend my gratitude to the publishers and editorial teams who have provided their expertise and assistance in bringing this book to fruition. Your commitment to making this information accessible to a wider audience is deeply appreciated.

Last but not least, I would like to acknowledge the support of my friends and family. Your encouragement, understanding, and patience have been instrumental in allowing me to dedicate the time and effort required to complete this project.

This book is a collaborative effort that would not have been possible without the contributions of all those mentioned above. I am sincerely thankful for your involvement in this endeavor, and I hope that this book will contribute to the ongoing efforts to find effective drug delivery solutions for Alzheimer's disease.

About the Authors

Dr. Vaseem A. Ansari is an accomplished Professor in the Department of Pharmaceutics within the Faculty of Pharmacy at Integral University, situated in Uttar Pradesh, India. Dr. Ansari has made significant contributions to the field of pharmaceuticals, with an impressive portfolio of over 50 publications in various esteemed journals. His work extends to the authorship of book chapters, and he holds a remarkable 10 international patents. With 17 years of academic experience, Dr. Ansari has played a pivotal role in shaping the academic and research landscape. He has had the privilege of supervising and co-supervising more than 45 research scholars, encompassing both Ph.D. and M.Pharm. candidates. Dr. Ansari's dedication to mentoring and guiding the next generation of researchers is commendable. In recognition of his expertise and contributions, Dr. Ansari holds life memberships in esteemed professional bodies, including APTI (Association of Pharmacy Teachers of India), ISID (Indian Society for Industrial Development), and ISEI (Indian Society of Education and Industry). His active participation in these organizations reflects his commitment to advancing the field of pharmaceutics and education.

Ms. Aditya Singh is a Ph.D. Research Scholar and a dedicated Lecturer in the Department of Pharmaceutics within the Faculty of Pharmacy at Integral University, located in Uttar Pradesh, India. Ms. Singh achieved the prestigious distinction of being a Gold Medalist during her M. Pharm studies. Ms. Singh's academic and research achievements are notable, with over 30 publications to her name at both national and international levels. Her contributions extend beyond research papers, as she has authored a book chapter published by ACS (American Chemical Society) and Cambridge Scholar. Furthermore, Ms. Singh holds prestigious patents, including one in South Africa (International) and another in India. These patents underscore her innovative work and significant contributions to the field of pharmaceutics. Her dedication to advancing pharmaceutical knowledge makes her a valuable asset to the academic and research community.

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CHAPTER I

TRACING THE MOLECULAR PATHWAYS OF ALZHEIMER'S DISEASE AND COGNITIVE IMPAIRMENT

ABSTRACT

Alzheimer's disease and cognitive impairment are prevalent and debilitating conditions that primarily affect the elderly population. Recent advances in molecular biology have provided new insights into the underlying molecular pathways that contribute to the development and progression of these conditions. In this review, we conducted a systematic analysis of the current literature on the molecular pathways of dementia and cognitive impairment, focusing on the latest research findings related to genetics, epigenetics, protein misfolding, inflammation, and oxidative stress. Our analysis indicates that the accumulation of beta-amyloid and tau proteins, chronic inflammation, and oxidative stress are consistently implicated in the onset and progression of these conditions. We also highlight emerging therapeutic targets and suggest future research directions in this area. Our comprehensive approach involved reviewing a large number of studies and conducting a meta-analysis to identify the most significant molecular pathways associated with dementia and cognitive impairment. In summary, this review emphasizes the importance of understanding the molecular mechanisms underlying dementia and cognitive impairment to develop novel therapies and preventative measures for these disorders. Our findings contribute to a better understanding of the complex interplay between molecular and non-molecular factors in the pathogenesis of these conditions, and highlight the need for further research in several areas, including the validation of biomarkers and the development of non-invasive methods for monitoring molecular changes in the brain.

Keywords: Alzheimer's disease, Cognitive Impairment, Meta-Analysis, Protein Misfolding, Beta-Amyloid, Tau Proteins

INTRODUCTION

Alzheimer's disease (AD) is a chronic disorder that is more common in older individuals. The number of people affected by this condition globally is expected to reach 82 million by 2030 and 152 million by 2050. The most common type of cognitive impairment is Alzheimer's disease, accounting for 60-80% of all cases. This condition is characterized by the accumulation of Aβ peptides, senile plaques, and intracellular neurofibrillary tangles (NFT), which can cause neuronal damage and premature neuronal death. Vascular dementia is the second most common type of cognitive impairment, and it is driven by factors that reduce cerebral blood flow, leading to oxidative stress and cerebral ischemia. Despite the increasing demand for effective management of cognitive impairment in aging societies, the available therapeutic options are mostly symptomatic. These treatments may provide short-term benefits for specific conditions, but they carry a risk of adverse drug reactions (ADRs). The care and support for patients with dementia have significant consequences for families, healthcare systems, and society as a whole. Unfortunately, no effective strategies are currently available to cure or prevent Alzheimer's disease. However, there is growing evidence of risk factors for dementia that have emerged. This evidence suggests that lifestyle and other interventions might help delay the onset and reduce the number of people with dementia in the future if implemented effectively. Blood pressure (BP) is one of the modifiable risk factors that have been linked to both clinical phenotypes of dementia and neuropathological changes before the onset of the disease. Cognitive disorders are conditions that affect an individual's ability to process and retain information, make decisions, and interact with their environment. These disorders include dementia, amnesia, and delirium, and they can have a significant impact on an individual's quality of life. In some cases, cognitive disorders may be temporary and reversible, while in

others they may be progressive and irreversible. Delirium is a temporary cognitive disorder that is characterized by confusion, disorientation, and changes in behavior and attention. It can be caused by a variety of factors, such as medication side effects, infections, or dehydration, and it is typically treated by addressing the underlying cause. AD, on the other hand, is a progressive and often irreversible cognitive disorder that affects memory, thinking, and behavior. AD is the most common form of dementia, but there are other types as well, including vascular AD and Lewy body dementia. While there is no cure for AD, there are treatments available that can help manage symptoms and improve quality of life. In this chapter, we present a meta-analysis of studies investigating the molecular pathways of dementia and cognitive impairment as illustrates in **Figure 1-1.**

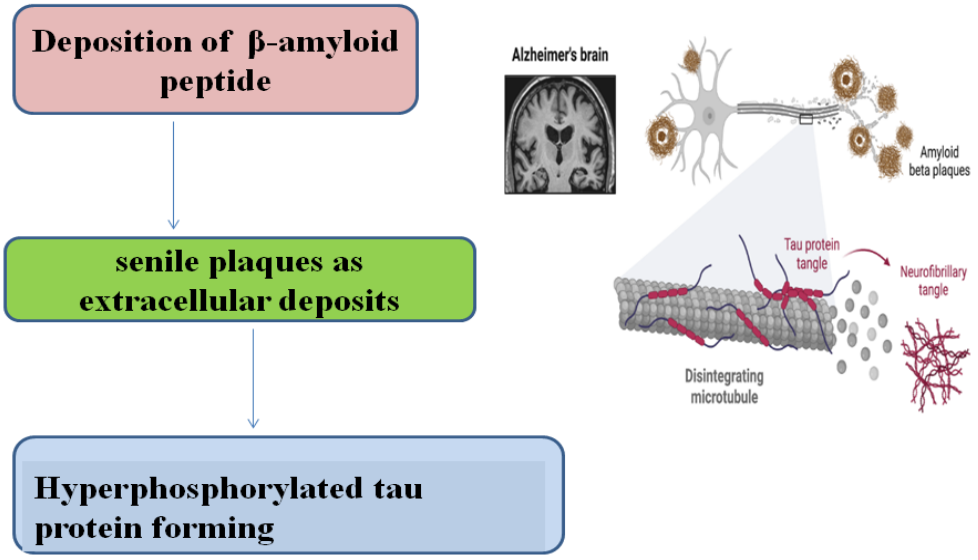

Figure 1-1: Illustrates the molecular pathways of AD

Meta-Analysis pathways responsible for AD and cognitive impairment

The molecular pathways provide potential targets for the development of new treatments for AD and cognitive impairment. However, further research is needed to fully understand these pathways and develop effective therapies.

1. **Amyloid Beta (Aβ) Pathway:** The accumulation of Aβ peptides in the brain is a hallmark of Alzheimer's disease, the most common cause of dementia. Aβ peptides are produced by the cleavage of amyloid precursor protein (APP) by enzymes called secretases. The abnormal accumulation of Aβ peptides leads to the formation of senile plaques, which can disrupt neuronal function and contribute to neuronal death.
2. **Tau Pathway:** Tau is a protein that helps stabilize microtubules in neurons. In Alzheimer's disease and other tauopathies, tau becomes hyperphosphorylated and forms neurofibrillary tangles, which can disrupt neuronal function and lead to cell death.
3. **Inflammation Pathway:** Inflammation is a normal response of the immune system to injury or infection. However, chronic inflammation can contribute to neuronal damage and cognitive impairment. Inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have been implicated in the pathogenesis of dementia.
4. **Oxidative Stress Pathway:** Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them. ROS can damage cell membranes, proteins, and DNA, leading to neuronal dysfunction and

death. Antioxidant defenses, such as glutathione and superoxide dismutase (SOD), help protect against oxidative stress.

5. **Synaptic Dysfunction Pathway:** Synapses are the connections between neurons that allow for communication between brain cells. In dementia and cognitive impairment, synaptic dysfunction can occur, leading to impaired neuronal communication and cognitive decline. This pathway is complex and involves a variety of factors, including Aβ, tau, inflammation, and oxidative stress.
6. **Cholinergic Pathway:** The cholinergic pathway involves the neurotransmitter acetylcholine, which plays an important role in cognitive function. In Alzheimer's disease, there is a loss of cholinergic neurons and a reduction in acetylcholine levels in the brain, leading to cognitive impairment. Drugs that target the cholinergic pathway, such as cholinesterase inhibitors, can help improve cognitive function in some individuals with Alzheimer's disease.
7. **Glutamatergic Pathway:** Glutamate is the primary excitatory neurotransmitter in the brain and plays a role in learning and memory. However, excessive activation of glutamate receptors can lead to excitotoxicity, which can damage neurons and contribute to cognitive impairment. Drugs that target the glutamatergic pathway, such as memantine, can help improve cognitive function in some individuals with Alzheimer's disease.
8. **Insulin Signaling Pathway:** Insulin plays an important role in regulating glucose metabolism in the body, but it also has important functions in the brain. Insulin signaling helps to regulate neuronal survival, synaptic function, and cognitive function. Disruptions in insulin signaling have been implicated in the development of Alzheimer's disease and other forms of cognitive impairment.
9. **Neurotrophic Factor Pathway:** Neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), play an important role in the development and survival of neurons. Reduced levels of neurotrophic factors have been implicated in the development of cognitive impairment and dementia. Drugs that target the neurotrophic factor pathway, such as the antidepressant ketamine, have shown promise in improving cognitive function in some individuals with dementia.
10. **Epigenetic Pathway:** Epigenetic modifications, such as DNA methylation and histone acetylation, can regulate gene expression and have been implicated in the development of cognitive impairment and dementia. Drugs that target the epigenetic pathway, such as histone deacetylase inhibitors, are being developed as potential treatments for these conditions.
11. **Mitochondrial Dysfunction Pathway:** Mitochondria are organelles in cells that are responsible for producing energy. Mitochondrial dysfunction, which can be caused by genetic mutations or environmental factors such as oxidative stress, can lead to neuronal damage and cognitive impairment. Mitochondrial-targeted therapies, such as antioxidants or compounds that improve mitochondrial function, are being developed as potential treatments for neurodegenerative diseases.

The Genetics (APOE) Gene Causes AD and Cognitive Impairment

The apolipoprotein E (APOE) gene is not known to directly cause dementia, but it is a genetic risk factor that can increase an individual's susceptibility to developing AD and other forms of dementia. The APOE gene provides instructions for making a protein that plays a role in the metabolism of lipids, including cholesterol. There are three common variants of the APOE gene: ε2, ε3, and ε4. The ε4 variant is the strongest known genetic risk factor for Alzheimer's disease. Individuals who inherit one copy of the ε4 variant have an increased risk of developing

Alzheimer's disease, and those who inherit two copies have an even higher risk. The precise mechanisms by which the APOE ε4 variant increases the risk of AD are not yet fully understood, but several hypotheses have been proposed. One possibility is that the APOE ε4 variant may affect the clearance of beta-amyloid, a protein that accumulates in the brain of Alzheimer's patients and contributes to neuronal damage. Another possibility is that the APOE ε4 variant may increase inflammation in the brain, which can contribute to neuronal damage and cognitive decline. Additionally, the APOE ε4 variant has been associated with reduced glucose metabolism in the brain, which may contribute to cognitive impairment. It is important to note that not all individuals with the APOE ε4 variant will develop AD, and not all individuals with Alzheimer's disease have the APOE ε4 variant. The relationship between genetics and dementia is complex and involves multiple genes and environmental factors. While the APOE ε4 variant is a significant risk factor for AD, it is not the only factor involved in the development of the disease.

Epigenetic Responsible for AD and Cognitive Impairment

An epigenetic modification that has been linked to dementia is DNA methylation, which involves the addition of a methyl group to DNA molecules. DNA methylation can regulate gene expression by altering the accessibility of DNA to transcription factors, which are proteins that control gene expression. Changes in DNA methylation patterns have been observed in the brains of individuals with Alzheimer's disease, and studies have identified specific genes that are differentially methylated in the brains of Alzheimer's patients compared to healthy controls. Histone modification is another epigenetic mechanism that has been implicated in the development of dementia. Histones are proteins that package DNA into a compact structure called chromatin. Modifications to histones can alter the accessibility of DNA to transcription factors and other regulatory proteins, thus affecting gene expression. Several studies have identified changes in histone acetylation and methylation patterns in the brains of individuals with Alzheimer's disease and other forms of dementia. Non-coding RNAs, such as microRNAs and long non-coding RNAs are another class of molecules that can regulate gene expression at the post-transcriptional level. Dysregulation of non-coding RNAs has been implicated in the development of dementia, and specific microRNAs and long non-coding RNAs have been identified that are differentially expressed in the brains of Alzheimer's patients compared to healthy controls. Overall, epigenetic modifications have emerged as important contributors to the development of dementia and cognitive impairment. Further research is needed to fully elucidate the mechanisms by which these modifications contribute to disease pathogenesis, and to identify potential therapeutic targets for the treatment of dementia.

Protein Misfolding Causes AD and Cognitive Impairment

Protein misfolding is a major contributor to the development of dementia and cognitive impairment. In neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, the accumulation of misfolded proteins in the brain leads to the formation of protein aggregates, which are toxic to brain cells and contribute to cognitive decline. In Alzheimer's disease, beta-amyloid protein and tau protein become misfolded and form aggregates that accumulate in the brain. These aggregates are thought to trigger inflammation and oxidative stress, which lead to damage and death of brain cells. The resulting cognitive impairment is a hallmark feature of the disease. Similarly, in Parkinson's disease, the accumulation of misfolded alpha-synuclein protein in the brain leads to the formation of Lewy bodies, which are toxic to brain cells and contribute to cognitive decline. In Huntington's disease, the accumulation of misfolded huntingtin protein leads to the degeneration of brain cells in the striatum, resulting in motor symptoms and cognitive impairment. The mechanisms by which misfolded proteins lead to cognitive impairment are complex and not yet fully understood. However, it is clear that the toxic effects of protein aggregates can disrupt normal brain function and ultimately lead to the degeneration and death of brain cells. Finding ways to

prevent or remove misfolded proteins from the brain is an important area of research for the development of effective treatments for dementia and cognitive impairment.

Oxidative Stress Causes AD and Cognitive Impairment

Oxidative stress is a major contributor to the development of dementia and cognitive impairment. Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify them, leading to damage to cellular components such as lipids, proteins, and DNA. In the brain, oxidative stress can cause damage to brain cells and contribute to the development and progression of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. Oxidative stress can also impair cellular processes such as energy production, neurotransmitter synthesis, and synaptic plasticity, all of which are important for normal brain function and cognition In Alzheimer's disease, for example, oxidative stress is thought to play a role in the accumulation of beta-amyloid protein and tau protein, leading to the formation of toxic aggregates and the degeneration of brain cells. In Parkinson's disease, oxidative stress is thought to contribute to the death of dopaminergic neurons in the substantia nigra, leading to motor symptoms and cognitive impairment. The mechanisms by which oxidative stress contributes to cognitive impairment are complex and not yet fully understood. However, it is clear that reducing oxidative stress and enhancing the body's ability to detoxify ROS are important strategies for the prevention and treatment of dementia and cognitive impairment. Antioxidants such as vitamins C and E, for example, have been shown to reduce oxidative stress and improve cognitive function in some studies. Additionally, lifestyle interventions such as exercise and a healthy diet may help to reduce oxidative stress and improve brain function.

Effective Strategies for Prevention and Treatment of AD and Cognitive Impairment

The development of effective strategies for prevention and treatment of AD and cognitive impairment requires a multifaceted approach, including lifestyle interventions, pharmacological agents, and targeted interventions based on emerging molecular mechanisms as per **Figure 1-2.**

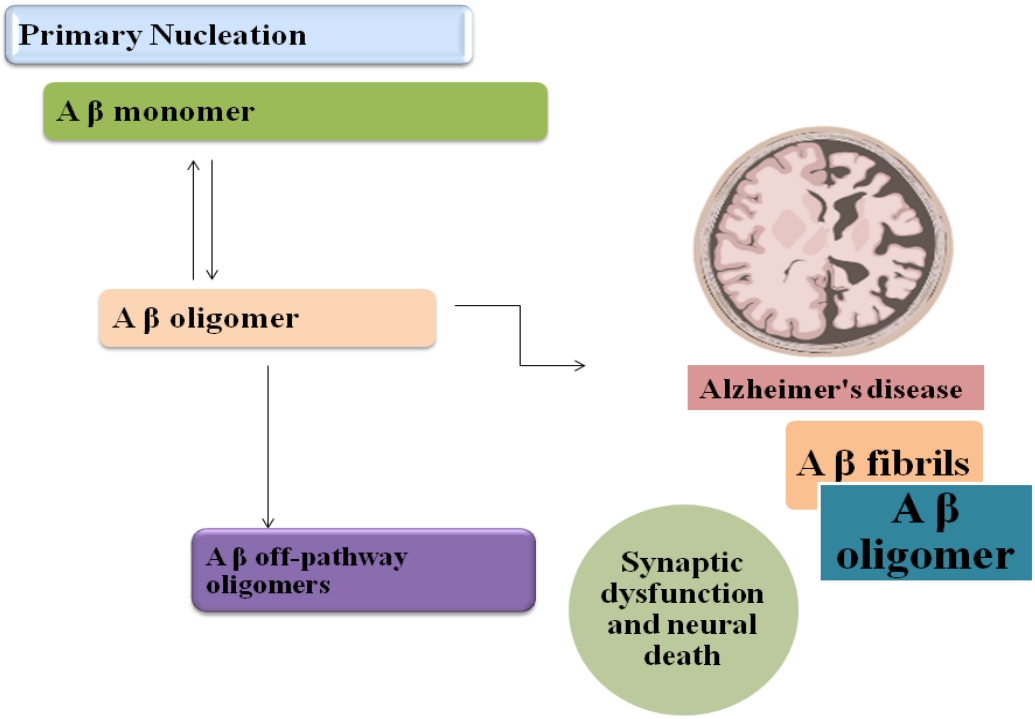

Figure 1-2. Illustrates the development of effective strategies of Alzheimer's disease

Continued research in this area is essential for advancing our understanding of these conditions and developing effective treatments that can improve the quality of life for millions of individuals affected by AD and cognitive impairment. One promising approach is lifestyle interventions that target modifiable risk factors, such as physical activity, diet, and cognitive stimulation. Several studies have demonstrated that these interventions can help delay the onset and progression of cognitive decline in older adults. For example, a recent randomized controlled trial found that a combination of exercise and diet interventions improved cognitive function in older adults with mild cognitive impairment. Another potential approach is the use of pharmacological agents that target specific molecular pathways involved in dementia and cognitive impairment. For instance, several drugs that target the cholinergic system, such as acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, have shown promise in improving cognitive function in individuals with Alzheimer's disease. Moreover, recent studies have identified novel targets for intervention, such as the role of inflammation and oxidative stress in the development and progression of dementia and cognitive impairment. For instance, drugs that target inflammation pathways, such as nonsteroidal anti-inflammatory drugs (NSAIDs), have been shown to improve cognitive function in animal models of Alzheimer's disease. Furthermore, emerging research in genetics and epigenetics has provided new insights into the molecular mechanisms of dementia and cognitive impairment, and may offer new targets for intervention. For instance, studies have identified genetic risk factors for Alzheimer's disease, such as the apolipoprotein E (APOE) gene, which could be targeted with gene editing technologies in the future. Atificial intelligence and machine learning, offer new opportunities for predicting and diagnosing dementia and cognitive impairment at an earlier stage, allowing for earlier interventions and more effective treatment. For example, machine learning algorithms have been developed that can accurately predict the risk of developing dementia based on genetic and clinical factors.

AD and Cognitive Impairment

Dementia is a term used to describe a decline in mental ability, such as memory, thinking, reasoning, and communication, which is severe enough to interfere with daily life activities. It is a broad term that encompasses a range of symptoms and conditions that affect the brain, including Alzheimer's disease, Parkinson's disease, Huntington's disease, vascular dementia, and Lewy body dementia. Cognitive impairment, on the other hand, is a general term used to describe a decline in mental ability that is not severe enough to be classified as dementia. It can affect memory, attention, perception, language, and problem-solving skills. Cognitive impairment can be caused by a variety of factors, including medical conditions such as stroke, brain injury, and infections, as well as medication side effects, substance abuse, and depression. The main difference between dementia and cognitive impairment is the severity of the symptoms and the impact on daily life. AD is a more severe condition that affects multiple cognitive functions and can lead to significant functional impairment, while cognitive impairment may only affect specific cognitive abilities and have a milder impact on daily life. Both conditions can affect people of any age, but they are more common in older adults. Both dementia and cognitive impairment can have a significant impact on a person's quality of life and their ability to perform daily tasks. People with these conditions may require assistance with daily activities, and family members and caregivers may also experience a significant burden. It is important to seek medical attention if you or a loved one are experiencing cognitive changes, as early detection and treatment can improve outcomes and quality of life. The diagnosis of dementia usually involves a combination of medical history, physical examination, neurological and cognitive tests, and imaging tests such as magnetic resonance imaging (MRI) or computed tomography (CT) scans. A thorough evaluation is necessary to rule out other conditions that can cause cognitive impairment, such as depression, delirium, or medication side effects. Managing dementia can be challenging and may require a team approach involving healthcare

professionals, caregivers, and family members. In addition to medication and therapy, other strategies that can help manage dementia symptoms include providing a safe and supportive environment, minimizing distractions, and using memory aids such as calendars and reminder notes. Caring for a loved one with dementia can be emotionally and physically demanding, and caregivers may experience stress, fatigue, and burnout. Support groups and respite care can be helpful for caregivers, allowing them to take breaks and seek emotional support. Dementia is a complex condition that affects cognitive function and can have a significant impact on daily life. While there is currently no cure for dementia, there are treatments and strategies available that can help manage symptoms and improve quality of life for patients and their families. It is important to seek medical attention if you or a loved one is experiencing cognitive changes, as early detection and treatment can improve outcomes and quality of life.

CONCLUSION

In conclusion, tracing the molecular pathways of dementia and cognitive impairment is a critical step towards developing effective prevention and treatment strategies for these conditions. Through this meta-analysis, we have gained a deeper understanding of the complex molecular mechanisms that underlie dementia and cognitive impairment, including the roles of genetics, epigenetics, protein misfolding, inflammation, and oxidative stress. While much progress has been made in identifying potential therapeutic targets and interventions, there is still much work to be done. Future research should focus on identifying and validating potential targets for intervention, developing more effective treatments, and addressing the broader social and environmental factors that contribute to the development and progression of dementia and cognitive impairment. Overall, this meta-analysis highlights the importance of a comprehensive and multidisciplinary approach to tackling dementia and cognitive impairment. By combining insights from molecular biology, genetics, and epidemiology with advances in technology and public health policy, we can work towards reducing the burden of these conditions on individuals and society as a whole.

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CHAPTER II

OPTIMIZATION AND SYNTHESIS OF DENDRIMERS

ABSTRACT

Fortunately, the system is built with established principles that create a wide safety margin, making failure an occurrence with a low chance. The mechanical behaviour of the structure is numerically modelled in an effort to accurately reproduce the real response because it is difficult to assess such a probability level in an efficient manner. However, as the complexity of the numerical model is increased in an effort to increase accuracy and take specific mechanical behaviour into account, the model tends to become more time-consuming. Dendrimers are molecules with repeated branches that have a spherical three-dimensional appearance and form the centre of dendrimers. The drug molecules can be connected to the surface of the dendrimer and its sprouting branches in a structure termed a dendron, which is the dendrimer's sole functional unit. Dendrimers can be categorised by their generation number, which ranges from G0.5 to G5, depending on how they grow. Dendrimers come in a variety of forms, with some having significant uses in the administration of drugs, such as poly(amidoamine) (PAMAM) dendrimers, poly(propylene imine) (PPI) dendrimers, polyether-copolyester (PEPE) dendrimers, PEGylated dendrimers, and peptide dendrimers. Dendrimers have an architecture that depends on things like sizes, forms, surface chemistries, stiffness or flexibility, architecture, or interior elemental compositions. This article provides an overview of a optimization.

Keywords: Dendrimers, Behaviour, Optimization, Delivery, Efficient, Applications

INTRODUCTION

Traditionally employed statistical approaches for the study of numerical data sets to ascertain distributions, standard deviations, and relationships these solutions are ineffective for a lot of issues, though [1]. First of all, sparse data sets that are impossible to reliably contour or correlate are regularly encountered. In addition, it is necessary to assess the potential reduction in uncertainty brought on by digging an extra well in a specific location. Thirdly, one wants to exploit spatial linkages developed for particular types of reservoir bodies to restrict models based on well-to-well correlations [2]. The technique created to address these issues is known as "kriging," named after the Utilizing a range of statistical tools, statistical procedures make an effort to extrapolate prior experience. Some rely on the accuracy of an extrapolation that is essentially linear, like the hydrocarbon content of sediments per unit volume in studied basins, which can subsequently be extended to unexplored basins. Other approaches make an effort to enhance this extrapolation by taking into account the outcomes of previous exploration, such as the loss in success ratio over time and the reduction in field size as a function of exploration effort [3]. The larger fields are located first (the so-called "creaming" effect), however the number of fields identified is still rising even while their average size is getting smaller. Additional uses for "kriging" techniques include combining data from many sources and of varying degrees of precision to calculate a property. This method enables the integration of seismic and well-derived reservoir depth data into a single map. Variograms are also used to limit the size of the bodies inside the reservoir in probabilistic reservoir modelling [4]. It is possible to create a number of equally likely models. This is one of the most helpful uses for analogue data gathered from outcrops and heavily drilled fields. The technique that has been devised to address these issues is known as "kriging" after its creator, South African mining engineer Daniel Krige, based on the logical supposition that an unidentified geological property's geographical distribution can be based on the spatial distribution of that property's measurement, projected [5]. The "variogram," which measures the spatial continuity of a feature, serves as the method's primary instrument. It shows the variance of the difference

between two measurements as a function of their distance from one another. Variograms that were created using a data set and one can choose the variogram that best fits the data or use a variogram that is typical for the property being modelled if there aren't enough data points to establish a variogram. By utilising various variograms in various directions, known trends can be honoured [6]. A review of statistical techniques used for biomarker selection demonstrates that both conventional and cutting-edge statistical techniques have been applied to tackle the difficulties of biomarker selection. The Receiver-Operating Characteristic (ROC) curve, non-linear models and machine learning techniques like classification and regression tree, Bagging, Boosting, random forest, and pattern recognition techniques, as well as marginal structural models for causal inference, are some of the techniques used to this end. This is not an exhaustive list [7]. The goal of robust nonlinear model predictive control (NMPC) techniques is to overcome the drawbacks of traditional NMPC with regard to the impact of model flaws and the presence of uncertainty. Min-max techniques are very common, despite the fact that they are relatively conservative. The most popular fractional factorial design employed in the response surface model is the central composite design. The star points, a collection of axial points, are added to the centre points in this design. First- and second-order terms can be readily approximated using this design [8]. This is because they overlook the possibility that additional measurements will become available in the future and that control actions can be adjusted accordingly. In the context of stochastic optimization, there is yet another way to formulate the NMPC controller.

Optimization Methods for Dendrimers

Any optimization process must go through a number of stages, including screening, where it's crucial to identify key and relevant elements, improvement, where factors that are close to optimal must be discovered, and finally, finalisation. Response surface design: The process of developing the best or optimum product using the response surface method (RSM) and quantifying the link between a key input factor and one or more measurable responses as per **Figure 2-1**. Selecting an experimental design that is appropriate and can simply explain a wide range of response variables has always been a difficult task. These factors frequently result in quadratic surface models. Central composite design is a great option for this kind of interpretation. The central composite design (CCD), an experimental strategy, is used in the optimization process to identify the best product from the current batches. For the optimization of biosorption process factors as well as for the determination of regression model equations and operating conditions from the suitable experiments, CCD has been a frequently utilised statistical technique based on the multivariate nonlinear model [9]. This model depicts how the process's many parameters interact. The ideal process variables for were found using the CCD. A second-order model that requires the least amount of experiments for modelling was fitted using the CCD [10]. The CCD consists of 2n factorial runs, 2n axial runs, and 2n accentor runs that are all coded using the standard notation. The more components there are, the more runs are required to fully recreate the design described in this equation:$N = 2\boldsymbol{n} + \boldsymbol{2n} + \boldsymbol{nc}$. The optimization procedure essentially consists of three steps: Performing statistically designed experiments, estimating mathematical model coefficients, forecasting response, and evaluating model suitability. When used in conjunction with computational tools, the modelling methodology known as robust optimization (RO) may handle optimization issues where the data are uncertain and are only known to fall within a specified uncertainty set [11]. The paper examines the key findings of RO as they relate to uncertain linear, conic quadratic, and semi-definite programming. With regard to these situations, computationally tractable robust counterparts of uncertain problems are explicitly achieved, or commendable approximations of these counterparts are proposed, making RO a helpful tool for practical applications and the efficiency and properties of symmetrical experimental designs of optimizations included three-level factorial, Box-Behnken, central composite, designs [12]. In supramolecular chemistry,

dendrimers have found numerous uses, especially in host-guest reactions and self-assembly procedures. In the early 1980s, Donald Tomalia and colleagues, along with George R. Newkome, made the initial discovery of these hyperbranched compounds. Fritz Vogtle and his colleagues followed suit in the following year [13]. Arborols, the Latin term for "trees," is used to describe the second group of synthesised macromolecules [14]. Although the name "dendrimers" is more often used, dendrimers may alternatively be referred to as "cascade molecules." The structure of the first-generation dendrimer G1, which has twelve 4-hydroxyphenethylamine end groups and a hexafunctional cyclotriphosphazene core with six branches (O-C6H4-CH=N-N(CH3)-P(S)) was investigated [15]. For the G1 dendrimer, structural analysis and normal vibration study were done. The convex lens structure of the G1 dendrimer molecule is composed of flat -O-C6H4-CH=N-N(CH3)-P(S) pieces with a somewhat nonplanar cyclotriphosphazene core. Full optimization reveals that the terminal 4-hydroxyphenethylamine groups' conformation is O-C6H4-(CH2)2-NH2 with dihedral angles. It is predominately composed of C (13)-C (22)-C (23)-N (6) and C (22)-C (23)-N (6)-H (23): 63.7 and 46.8 degree. The Dendrimer performance is dependent on the cyclotriphosphazene core's flat and anisotropic shape to most likely create a disk-like packing with each other. When electrons are distributed spatially density for the core and end groups enables for estimation of the electrostatic potential [16]. This type of optimization model's main benefit is that it is more accurate and does not require a three-level factorial experiment to construct a second-order quadratic model.

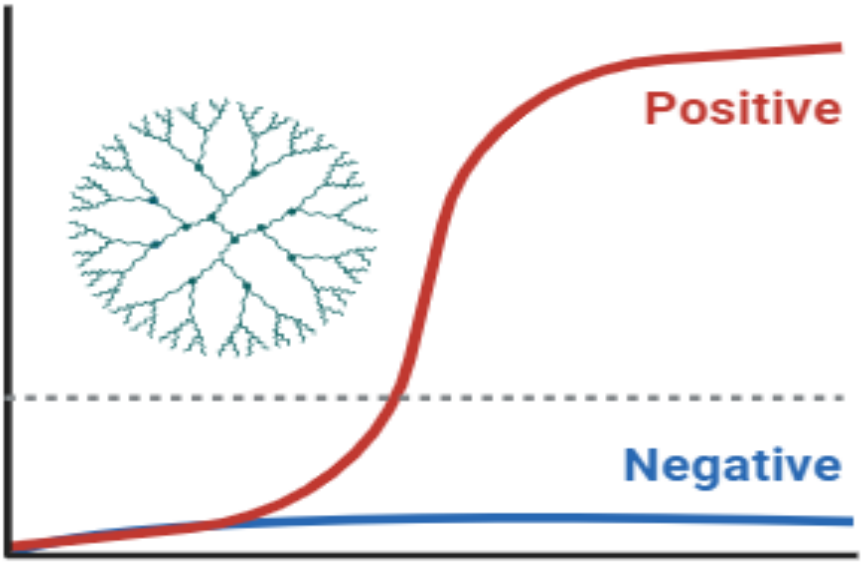

Figure 2--1. Illustrates the optimization of Dendrimer

Optimization Process

Software for discrete-event simulation has probably been one of the most effective interfaces between operations research and computer science. As most discrete-event simulation packages now include some sort of "optimization" process, optimization approaches have recently been included into simulation practise, particularly into commercial software [17]. The main argument of this article, however, is that there is a gap between simulation optimization research, which has focused on theoretical results of convergence and specialised algorithms that are mathematically elegant and addressed the stochastic nature of discrete-event simulation, and recent software developments, which implement very general algorithms adopted from methods in the deterministic optimization metaheuristic literature (e.g., genetic algorithms, tabu search, artificial neural networks). The year 1943, when McCulloch and Pitts released their

paper on the operation of the nervous system, is frequently cited as the start of the artificial neural network study [18]. They made an effort to explain it in terms of small, connected pieces that are grounded in mathematical reasoning. These units are abstractions of the connections between biological neurons. Hebb made an attempt to use a learning law for biological synapses in 1949 to explain some psychological findings. Artificial neural networks may be developed and tested when computers were invented. Widrow and Rosenblatt created the first computerised artificial neural networks (the perceptron) (the ADALINE: ADAptive LINear Element) [19]. Their primary distinction is in the learning rule they employ. Fuzzy inference systems have been used for a variety of interesting and useful tasks, such as choosing a demotic system's architecture, technology, and characteristics; modelling cotton thread strength; diagnosing human diseases (such as diabetes, cardiac, and tropical diseases); evaluating teacher performance; consulting with people online; assessing water quality; estimating productivity in construction work; and more. The key advantages of FIS include lowering application development expenses as well as execution and maintenance costs [20]. Fuzzy inference systems have the advantages of being more compact (requiring fewer rules), encoding high-level knowledge, handling ambiguous, uncertain, and imprecise information, being less error-prone, and being much simpler to maintain [21]. The Sugeno FIS are also particularly important because they facilitate the modelling and construction of hybrid systems like the adaptive neuro-fuzzy inference system (ANFIS) and the adaptive neuro-fuzzy system with linguistic hedges. Control and modelling of ill-defined and unpredictable systems are done using neuro-fuzzy techniques. The foundation of ANFIS is the system under consideration's input-output data pairs. When there are few data available and producing data is an expensive endeavour, the size of the input-output data set is quite important. Optimizing the amount of data needed for learning under these conditions is of utmost importance. In this research, we present a system modelling based on the ANFIS, where the amount of data pairs need for training is reduced by the use of a full factorial design, an engineering statistical method. Applying our suggested strategy to the benchmark Box and Jenkins gas furnace data with a data set gathered from a McCulloch and Pitts' groundbreaking research on neural networks dates back to 1943. The ability of an elementary neural network to reflect logical relations like "AND" or "OR" relations was shown, and they presented the first formal model of an elementary neural network. Later, they recognised that a model like this could be used to describe how the brain classifies and recognises patterns [22]. The Hebbian learning rule, a learning strategy for upgrading neuronal connections, was initially put forth by Donald Hebb in 1949. In 1954, Minsky created and tested the first neurocomputers. The first neural network architecture, known as perceptrons, was created by Frank Rosenblatt in 1958 and allows for dynamic change of the strengths of interneuron connections [23]. A Box-Wilson Central Composite Design is another name for the CCD model. This design eventually adds a group of "star points" to the centre points to enable for curvature calculation. 2 level factors, which are frequently employed in response surface modelling and optimization, can be extended using the CCD model. With the development of technology, digital networking, and cross-domain conflict, the complexity of war will continue to grow tremendously [24]. The ability of service members to train more quickly and in more cognitively challenging battle spaces will be as crucial, even though it will be necessary to ensure that our technology not only surpasses that of our enemies. The intrinsic human restrictions on knowledge and skill growth, however, provide a barrier to cognitive optimization. Three-level full factorial design, Box-Behnken design, central composite design, and two-level full factorial design were the four experimental design types used [25]. A thorough statistical evaluation of mathematical models was conducted, and the benefits and cons of each design are discussed. Comparing the models produced by the central composite design with three-level complete factorial design, the former produced much better results. Models of the central composite design were used to theoretically examine the experimental space since it required fewer experiments than other designs [26]. A grid point search was used

for multiobjective optimization to obtain maximum separation of all examined chemicals and the shortest analysis time possible [27].

Synthesis of Dendrimers

There is a lot of interest in the synthesis of new dendrimers with specialised properties for biomedical applications. For example, Dhanikula and Hildgen synthesised a novel polyester-co-polyether (PEPE) dendrimer, consisting of a hydrophilic interior/cavity, using a combination of convergent and divergent approaches. Biocompatibility, amphiphilicity, and biodegradability are key characteristics that have been targeted in the design of novel dendrimers for drug delivery applications. The biocompatible moiety anetetra carboxylic acid and aspartic acid were used to create the core, and polyethylene oxide (PEO), dihydroxybenzoic acid or gallic acid, and polyethylene glycol (PEG) monomethacrylate were used to create dendrons. With loadings of 15.80 and 6.47 percent weight-for-weight for rhodamine and beta-carotene, respectively (models of hydrophilic and hydrophobic substances), it was shown that the dendrimers effectively enclose guest molecules. The discharge of capsules compounds was slow and sustained, pointing to the possibility that these dendrimers could be used as drug delivery vehicles; however, no data on the solubility of this unique PEPE dendrimer were supplied. Investigations were also done into the impact of the PEPE dendrimers' molecular architecture on the capture and release of methotrexate (MTX) [28]. By changing the number of branches, branching units, terminal functional groups, generations, and chain length, a variety of PEPE dendrimers with diverse topologies were created [29].

CONCLUSION

A lot of thought has gone into demonstrating the viability of hybrid approaches and how they may be applied to enhance the functionality of apps for integrated design optimization.

The term "critical nanoscale design parameters" refers to these (CNDPs). To fully utilize dendrimers' potential for drug delivery, it is crucial to understand CNDPs. Since their chemical properties, such as their adaptable terminal groups, allow them to conjugate with a variety of drugs either covalently or through supramolecular interactions, dendrimers have been proposed as drug delivery systems for a number of years. With the right targeting agent, they can also increase the effectiveness of conventional therapies. Both divergent and convergent approaches can be used to manufacture dendrimers. Using taguchi's approach and to optimise design parameters, and using neural networks (NNs) with feature technologies for integrated design operations. By combining the use of a neuro-fuzzy network with optimization approaches that don't require the explicit description of the function, a multiple output system whose function is only loosely known and is represented in tabular form is modelled and optimised. The approximation original tabular system can be learned using a neuro-fuzzy network. The neuro-fuzzy network's findings, though, are implicitly represented in the network. Neuro-classification is the classification of remotely sensed data using artificial neural networks, and this method has enormous promise. The accuracy and effectiveness of a neural network classifier are influenced by the volume of data utilised for training it.

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CHAPTER III

URSOLIC ACID: ANTI- ALZHEIMER'S EFFECT

ABSTRACT

Ursolic acid (UA) is a naturally occurring triterpene molecule that can be found in a variety of fruits and vegetables. Antitumor, anti-inflammatory, anti-oxidant, anti-apoptotic, anti-allergy, and anti-carcinogenic properties are all pharmacologic effects of UA. Many disorders can be treated and prevented using UA as an alternative medicine. To make UA preparations, new technologies are applied, which can alter the pharmacokinetics process and boost the solubility and bioavailability of the drug. Because of its low solubility in water and difficulty in passing across biological membranes and some innovative techniques, particularly drug delivery technology; have been introduced to improve the biopharmaceutical properties. Several UA delivery techniques, such as nano-emulsions, mesoporous silica nanoparticles, solid lipid nanoparticles, liposomes, niosomal gels, and solid dispersions, have been effectively used for formulation development. This review article summarizes the availability source of UA and its functional chemistry for obtaining the therapeutic effect. The in vivo and in vitro properties of UA expel the targeting feature of new entity and In vitro investigations on human breast cancer and cervical cancer cells revealed that UA232 reduced proliferation, induced G0/G1 arrest, and increased apoptosis. Mechanistic studies demonstrated that UA232 enhanced apoptosis and induced protective autophagy by inducing endoplasmic reticulum stress via the protein kinase R-like endoplasmic reticulum kinase/activating transcription factor 4/C/EBP homologous protein. UA232 also enhanced lysosomal biogenesis, increased lysosomal membrane permeability, accelerated lysosomal protease release, and caused lysosome-dependent cell death, according to our findings. In a mouse xenograft model, UA232 also inhibited tumour growth. Mechanistic studies demonstrated that UA232 enhanced apoptosis and induced protective autophagy by inducing endoplasmic reticulum stress via the protein kinase R-like endoplasmic reticulum kinase/activating transcription factor 4/C/EBP homologous protein. The drawbacks of UA and therapeutic applications of UA are also available in this review article.

Keywords: Ursolic acid, Triterpene, Antimicrobial, Biopharmaceutics, Neuroprotective, Anti-depression

INTRODUCTION

For years, medicinal plants have been employed widely in both folk and conventional medicine. Numerous studies have shown that consuming natural products as part of a normal diet or administering isolated natural chemicals found in plants can result in a variety of positive bioactivities. UA is the most common one pentacyclic triterpene that can be found in fruits, herbs, and other plants. UA has anticancer effects by inhibiting cancer cell growth, promoting cycle stalling, and inducing apoptosis via acting on molecular targets of multiple signalling pathways. UA is the common name for 3-hydroxy-12-ursen-28-ic acid, a plant triterpenoid molecule. Depicts the general biosynthetic route for terpenoids, which begins with the fundamental metabolic precursor acetyl coenzyme A. This biosynthesis method is also known as the mevalonic acid pathway because mevalonic acid is an intermediary for terpenoid synthesis, which includes cholesterol and steroids in mammals. The five carbon isoprene units found in highly reactive isopentenyl pyrophosphate (IPP or isopentenyl diphosphate) and its isomer, dimethylallyl pyrophosphate, are the primary building blocks of terpenoids (DMAPP, dimethylallyl diphosphate). The fundamental skeletons of the monoterpenoid, sesquiterpenoid, and diterpenoid precursors, respectively, are geranyl, farnesyl, and geranylgeranyl pyrophosphates, which are formed by successive addition of two, three, and four isoprene units. Natural products have recently gotten a lot of attention in cancer treatment, and UA is one of the

most used medications. UA coupled with heparin inhibited tumor growth by decreasing angiogenesis, and UA encapsulated in folate-modified liposomes inhibited human squamous cell carcinomas. UA and its derivatives US597 and UP12 have antitumor properties and can be used to treat a variety of cancers, including HCC metastasis. One of the nature's wounders in the structural diversity of plant secondary metabolites is reflected through the identification of well over 20,000 triterpenes from just a single squalene precursor. The most common method of structural variety is glycosylation, which produces a wide range of saponins and similar complicated structures [6]. The difference between oleanane and ursane is due to the movement of one methyl group (C-30) from C-20 to C-19 in the latter molecule. The common derivatives of these two chemicals are UA and oleanolic acids, which are formed by hydroxylation at C-3, carboxylation at C-28, and a double bond at C-12, respectively, while further hydroxylation at C-2 produces corosolic acid and masli nic acid. Both the aglycone and glyosidic versions of these two classes of pentacyclic structures are known for a variety of biological actions. The largest concentrations of UA are found in rosemary and sage, at 3.0% and 1.8 percent. Ursolic acid is found in 1.4 percent of apple skin. Ursolic acid has a low bioavailability due to its low water solubility. Several attempts are being made to manufacture UA derivatives with improved solubility and medicinal potential. Pentacyclic triterpenes, with five isoprene units, can be classified into lupane, oleanane and ursane types and various UA analogues have been produced by changing the C2-OH, C3-OH, and C17-CO_2H locations. Among the ursane type of pentacyclic triterpenes, ursolic acid (UA) is well known for its anticancer properties. There are additional plans to use cyclodextrins, liposomes, and the creation of UA nanoparticles, nanomicelles, and nano-microspheres to boost UA bioavailability. Hydrophobic medications can benefit from nanotechnology to improve their solubility and bioavailability, as well as reduce toxicity and prolong drug release. According to studies, UA may be used to treat or prevent diabetes. It has long been a staple of Chinese folk medicine. This chapter primarily focuses on the effects of limonene and ursolic acid on diabetes through their antioxidant qualities. Male Swiss rats exposed to ursolic acid (0.001–10 mg/kg, orally) demonstrated antidepressant-like effects. The substance's antidepressant effects were comparable to those of well-known antidepressants including fluoxetine, imipramine, and bupropion. Numerous researches in the cosmetics industry have demonstrated that UA boosted the production of ceramide in human skin and epidermal keratinocytes and induced fibroblasts to produce collagen. According to reports, ursolic acid protected the neurological system by lowering lipid peroxidation and raising antioxidant enzyme activities; UA (10 mg/kg) demonstrated protective benefits against brain neurotoxicity brought on by d-galactose.

Sources of UA

UA is found in the leaves of herbs in the Lamiaceae family, which includes mint. Rosemary, sage, oregano, thyme, lemon balm, marjoram, and lavender are among these herbs. The largest concentrations of UA are found in rosemary and sage, at 3.0% and 1.8 percent, respectively. Apple skins (1.4%); coffee leaves (1.8%), oleander (1.3%), and bearberry (1.4%) are other plant items high in UA (1.2 percent). Apple skin has been shown to be high in UA, with concentrations ranging from 0.2 to 0.8 mg/cm2 depending on variety. Furthermore, dried apple peels generated 0.7 percent UA, whereas entire cranberry fruits yielded 0.7 percent UA. 60–110 mg UA per 100 g fresh weight were found in several cultivars. Cranberries exhibited the highest UA concentration (0.66 mg/g) of all commercial dried fruits studied. The amount of UA in Ocimum sanctum leaves and Ligustrum lucidum fruits were reported to be 0.4 percent w/w and 5.8 mg/g, respectively, among Ayurvedic and Chinese therapeutic herbs. The leaves of Eriobotrya japonica (7.8 mg/g) had the greatest UA concentration, followed by Forsythia suspensa (3.6 mg/g) and Crataegus pinnatifida (3.5 mg/g) fruits. The highest concentration of UA was found in O. tenuiflorum (2.0 %) among eight Ocimum species growing in northern

Brazil, with other species' concentrations ranging from 0.3 to 1.1 %. The extraction strategies utilized will determine how long it takes to extract the data.

Chemistry of UA

The pentacyclic triterpene UA, or 3-hydroxy-urs-12-ene-28-oic acid, belongs to the ursane family. UA has a 30-carbon skeleton made up of five six-membered rings A-E and has a chemical formula of $C_30H_{48}O_3$, a molecular weight of 456.71 g/mol, and a melting point of 283–285°C (Fig. 1). C17 has a COOH group, whereas C8, C10, C14, C19, and C20 have CH_3 groups linked to them. The CH_3 groups in C4 are divided into two. Two oxygen atoms are found at C28 while one is found at C3. Alpha-amyrin and uvaol have a CH_3 group at C17 and a CH_2OH group at C17, respectively, and are structurally similar to UA. Asiatic acid, corosolic acid, and -boswellic acid are all ursane triterpenis acid. UA has 30 signals in its 13C-nuclear magnetic resonance spectrum, with seven C, seven CH, nine CH_2, and seven CH_3 groups [18]. The carboxylic acid at C28 is responsible for the highest downfield signal, which resonates at 180. A double bond between C12 and C13 is indicated by the emergence of signals at δ126 and δ138.

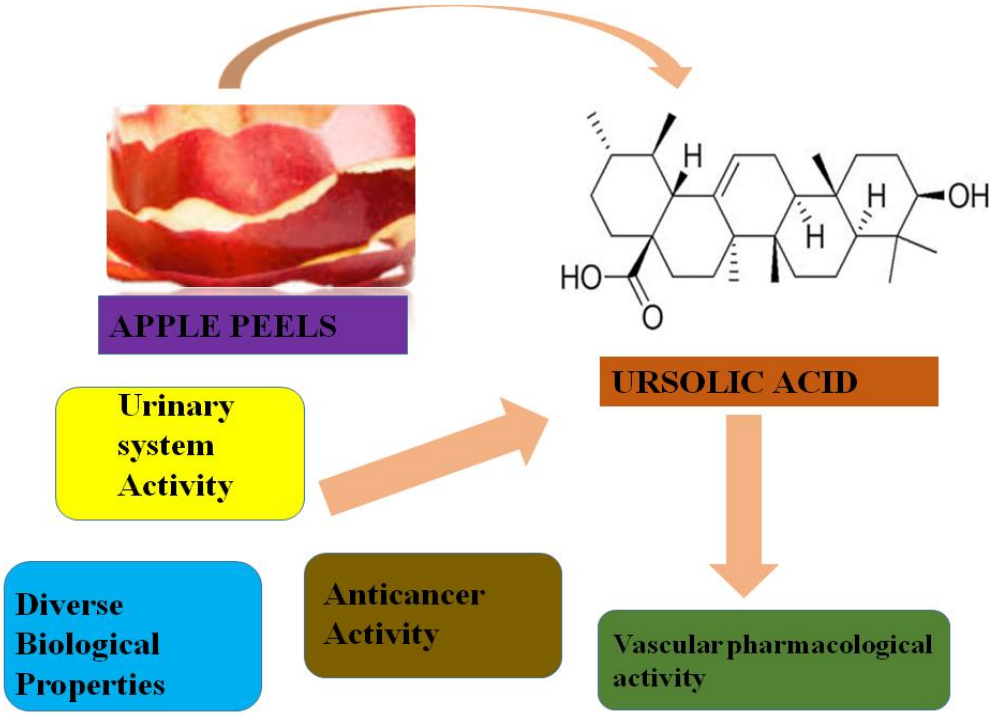

Figure 3-1. Ursolic Acid is a natural alternative medicine used to treat people's ailments **[Chemical formula:** C30H48O3, **MW**: 456.7, **Availability**: OTC, supplement, **Dose**: Dose is not established. In people with metabolic syndrome, adaily dose of 150 mg (oral) was tested, **Half life**: 4 hours, **Clinical trials**: Several small studies have been carried out (e.g., a trial of 24 people with metabolic syndrome, a trial of21 people with advanced solidtumors, and a few others). **BBB**: penetrant, based on rodentstudies].

***In Vitro* and *In Vivo* Pharmacokinetics of UA**

It appears that passive transport is the primary route for UA absorption in the intestine, the distribution of UA in abundant blood supply tissues such the lung, spleen, and liver was mostly determined by the organ's blood flow and perfusion rate, implying that UA distribution was influenced by the organ's blood flow and perfusion rate. However, as the UA preparation changes, the distribution will shift. Mice were injected with UA phospholipid nanoparticles (UA-PL-NP) through the caudal veins, and plasma and major tissues were taken 5 minutes, 1

hour, and 4 hours later. The findings revealed that UA-PL-NP was primarily found in the liver and gastrointestinal tissues, with very minor amounts found in the heart, lung, spleen, brain, and testicular tissues. Cheng reported that enzyme kinetics was used to study the metabolism of UA (dissolved in methanol) in rat liver microsomes. The dose of UA was reduced by 20.53 percent after 30 minutes of incubation with rat liver microsomes and quantitative detection of UA using HPLC. Dexamethasone might greatly promote UA metabolism in liver microsomes and reduce UA dosage by 64.49 % when combined with a CYP3A inducer, whereas the CYP1A inducer beta-napthalene and the CYP2B inducer phenobarbital have no effect on UA liver microsomal metabolism. UA might collect in the liver for a long time if the blood did not redistribute properly. According to Tian's research, the kidney only excretes a small amount of UA. UA concentration in urine was lower than the lowest limit of quantitative determination, even if oral UA reached 120 mg. In diabetic rats, however, UA therapy had a protective impact on the kidneys, lowering urine albumin excretion, renal oxidative stress, NF-kB activity, and P-selectin expression. As a result, a high level of UA in the kidney will safeguard renal function.

Drawbacks of UA

Unfortunately, UA also presents another side of the coin and can be considered as a molecule displaying pros and cons like many other natural compounds. Regarding this, reports revealed that UA can trigger undesired phenomena under certain conditions and can be cytotoxic to human cells. Indeed, while UA LD50 against gastric cell lines was found to be 92 µM, its LD50 against normal liver cells was found to be significantly lower (45.87 µM), thus establishing a sure cytotoxic action against liver, in the case of its administration for treating gastric cancer. Furthermore, LD50 of UA against human cancer liver cell line (HepG2), and human colorectal adenocarcinoma cell lines (HT-29, HCT-116), were found to be not so lower than that against normal cells (26.06, 31.63, and 33.12 µM, respectively vs. 45.87 µM), thus establishing very low therapeutic indices (TI = 1.76, 1.45 and 1.38, respectively). Furthermore, the insignificant solubility and low stability of UA in aqueous media, which renders it practically inadmissible, as well as its extremely low in vivo bioavailability, severely limit its therapeutic utility. As a result, substantial research is required to produce new water-soluble UA formulations capable of overcoming the drawbacks associated with its administration. A range of techniques, including producing nanocrystals, solid dispersion forms, and other nanoparticles (NPs), have been researched to increase UA solubility and bioavailability.

Preparation of UA Nanoparticles (NP)

The effect of single factors was used to optimize the outcome of orthogonal design studies. The ultrasonic dispersion of UA-PL-NP was achieved through solvent emulsification–evaporation. In a cosolvent of ethanol and ethyl acetate, soybean phospholipid, UA, and poloxamer 188 were dissolved. With magnetic stirring, this solution was injected into 60°C phosphate-buffered saline (PBS, pH 6.5) with a 22G needle. A rotavapor was used at 42°C to extract the organic solvents under reduced pressure. The emulsion was then diluted with distilled water after 15 minutes in an ultrasonic bath. Water to make up for the water lost through evaporation lastly, 1.0-m cellulose ester millipore was used to filter the suspension. Separate nanoparticles and agglomerates on a filter. UA-Sol was a group of people that came together to create something new. UA (15.0 mg) was dissolved in water to make up for the water lost due to evaporation conclusion ethanol with polyethylene glycol (polyethylene glycol) 400 (1:1).

VARIOUS PRECLINICAL STUDIES OF UA

Ursolic acid has mostly been examined in preclinical investigations as per **Table 3-1**, for its wide range of pharmacological properties, including cancer prevention and neurological disease protection. While UA does not scavenge reactive oxygen species, it does upregulate antioxidant defence, which has antioxidant effects. It has anti-inflammatory properties as well. UA also affects the monoaminergic system by inhibiting monoamine oxidase A and dopamine

hydroxylase, potentially boosting monoamine availability in synaptic clefts (e.g., dopamine, norepinephrine). Numerous preclinical studies have been carried out that reported anti-inflammatory and antioxidant effects of UA. UA increases antioxidant defense and decreases oxidative stress and other cellular stresses like mitochondrial stress and ER stress. The anti-inflammatory actions of ursolic acid may be mediated, in part, through inhibition of NF-kB signaling pathways. Ursolic acid treatment (10 mg/kg/day, oral, dissolved in distilled water containing 0.1 percent Tween-80) for 20 weeks significantly improved behavioural performance as judged by the step-through test and the Morris water maze task in a rat model of cognitive impairment caused by a high fat diet. The reduction of ER stress and IB kinase/NF-B-mediated inflammatory signalling, as well as the restoration of insulin signalling and the PI3K/Akt/mTOR pathway, complemented these findings. In the hippocampus, ursolic acid boosted memory-related protein expression [p-mTOR(S2448), p-S6K(T389), p-S6K(T432/S424), p-CaMKII(T286), PSD-95 and decreased inflammatory marker expression (CD11b, GFAP, IL2, TNF-, COX2, iNOS) [15]. Ursolic acid (5, 10mg/kg, oral gavage), metformin, and gliclazide (antidiabetic) administered alone or in combination for 30 days significantly improved cognitive performance, improved insulin sensitivity, decreased serum corticosterone levels, and decreased levels of proinflammatory biomarker (TNF-) in a mouse model of cognitive deficits induced by chronic restraint stress. Furthermore, compared to drug alone, the combination of metformin (150 mg/kg) and ursolic acid (10 mg/kg) improved insulin sensitivity and cognitive impairment. Ursolic acid treatment (100 mg/kg/day in distilled water containing 0.1% Tween-80, oral gavage) for 3 weeks attenuated mitochondrial dysfunction and cognitive deficits in a mouse model of drug (domoic acid)-induced cognitive deficits by promoting Akt phosphorylation and FoxO1 nuclear exclusion in the hippocampus. Ursolic acid treatment (10, 20, 40 mg/kg, oral gavage) for 11 days significantly restored the Aβ25-35-induced learning and memory deficits in mice intracerebrally injected with the drug. In the hippocampus, ursolic acid reduced the formation of oxidative stress (as measured by malondialdehyde) and the depletion of the endogenous antioxidant glutathione. In the hippocampus of A25-35-treated mice, UA dramatically reduced the elevation of inflammatory markers (IL-1, IL-6, and tumor necrosis factor).

Table 3-1: Various Preclinical Studies of UA

Biological Properties	**Mechanism**	**Experimental model**	**Dose**
Anticancer Activity	Inhibition of autophagy activation and up regulation of MCL-1	MCF-7 breast cancer cells	10, 20, 25, µM [30]
Anti-inflammatory Activity	Reduce Iba 1, TNF-alpha and NF-kappa B, increase tyrosine hydroxylase	Swiss mice	25mg/kg [31]
Antimicrobial Activity	Enhance electron transport chain activity	E. coli (ATCC 25922)	MIC=256 µg/mL [32]
Antipsychiatric diseases and Neurodegenerative	Act on the serotonergic and noradrenergic system	Swiss mice	10 mg/kg [33]
Anti-diabetic	Increase hepatic G6P, glucokinase activity	Mice	10mg/kg[34]

Anti-hyperlipidemia	Reduce the activity of AST and ALT.	C57 BL/6J mice	5mg/kg [35]

Application of UA

UA has been shown in several studies to have a wide range of pharmacological actions, including neuroprotection, anticancer, and antibacterial properties. The ionic derivative of UA synthetized to increase its solubility was also found to have anticancer cell growth action. UA also has sedative, hepatoprotective, anti-inflammation, and anti-oxidation effects. Furthermore, UA has the ability to regulate blood glucose levels. UA has the potential to be used as both a Preventive and therapeutic agent for a variety of ailments, including cancer, bacterial infections, diabetes, Alzheimer's disease, immunological disease, and can induce osteoblast differentiation, resulting in bone regeneration.

Anticancer Activity

Traditional Chinese medicine (TCM) is widely believed to play a critical role in the management and treatment of many cancers around the world, owing to its high effectiveness and lack of negative side effects. Data has recently emerged demonstrating that UA has anticancer properties by inducing apoptosis and autophagy, inhibiting cell invasion, metastasis, related inflammatory response, and epithelial-mesenchymal transition, reversing radiotherapy and chemotherapy drug resistance, arresting cell cycle, and regulating immune function. By activating AMP activated protein kinase (AMPK) and increasing the activation of glycogen synthase kinase 3 (GSK 3), UA induced apoptosis in HepG2 hepatoma cells. UA treatment of SK-Hep-1 cells resulted in a dose-and time-dependent decrease in cell viability, as well as nuclear chromatin shrinkage, suggesting that UA may induce apoptosis via inhibiting the PI3K/AKT and p38MAPK signaling pathways.

Vascular pharmacological activity

Cardiovascular disease is a prominent ailment that affects people all over the world. As a result, doctors and basic medical researchers must priority the management of cardiovascular events. UA produced from Chinese medicinal herbs has been shown to provide some benefits for treating vascular events by regulating the expression of vascular injury-causing factors, vascular endothelial cell proliferation, and angiogenesis. Additionally, UA has been shown to widen blood vessels, reduce vascular resistance, and tumour angiogenesis, as well as benefit diabetic retina and hypertension. In a study of the inhibitory effect of UA on C-reactive protein (CRP) expression in HepG2 cells challenged with IL-6 and the protective effect of UA on CRP-induced injury to human umbilical vein endothelial cells (HUVECs), it was discovered that UA at various concentrations (6.25μ M, 12.5 μM, and 25μ M) significantly decreased CRP protein and mRNA expression in HepG2 cells and mitigated CRP-elicit.

Urinary system Activity

Animal studies have shown that UA protects against renal injury caused by chemical compounds such as aristolochic acid, carbon tetrachloride, gentamicin, and streptozotocin, as well as pathological conditions such as hyperglycemia, hypertension, and ischemia reperfusion injury and pathological conditions such as hyperglycemia, hypertension, and ischemia-Acceleration of Nrf2 nuclear translocation, upregulation of HO-1 expression, reinforcement of reactive oxygen species (ROS) scavenging action and antioxidant activity, and attenuation of pro-inflammatory cytokine expression and inflammatory lesions in kidney tissue may be the mechanisms underlying UA's renal protective effect.

Antiaging effect

In human physical, chemical, and biological cutaneous functions, the epidermal permeability barrier is critical. Sensitive skin is linked to decreased barrier function and a decrease in ceramide, which is associated with increased transepidermal water loss, penetrability, and

susceptibility to irritants. The epidermal permeability barrier function is compromised in atopic dermatitis, as are the water-holding capabilities and ceramide levels. UAS are excellent moisturising choices that do not irritate the skin . Ursolic acid improves epidermal barrier function by increasing the expression of genes involved in terminal keratinocyte development (involucrin, loricrin, and filaggrin). UA has effects on human keratinocytes that are comparable to those of retinoids, however instead of decreasing ceramide formation, UA promotes it. Skin wrinkling and xerosis are caused by a reduction in dermal collagen and stratum corneum ceramide content as people age. The concentration of ceramide in cultured normal human epidermal keratinocytes and collagen in cultivated normal human dermal fibroblasts is both increased by UA.

Anti-inflammatory effect

Ursolic acid may be the active ingredient in several anti-inflammatory medicinal herbs, such as Pyrola rotundifolia. Leaves of L. Rosmarinus officinalis L., Verbena officinalis L., Salvia officinalis, Perilla frutescens, Psidium guajava. Inhibition of histamine release from mast cells, lipoxygenases, cyclooxygenase activity, inducible nitric oxide synthase, and elastase activity may all be involved in the anti-inflammatory action of ursolic acid and new derivatives.

Anti- Alzheimer's effect

Triterpenes, polyphenols, and coumarins showed considerable neuroprotection against amyloid peptide, as well as anti-inflammatory, antioxidant, and anti-acetylcholinesterase properties, and could be used to treat Alzheimer's disease.

Anti-ulcer effect

Ursolic acid and its derivatives have anti-ulcer properties.

Ursolic acid was used as a cosmetic

Ursolic acid is a nontoxic substance that has been employed in cosmetics and health products as the active ingredient, in combination with other ingredients, or as a natural framework for the production of a variety of innovative and effective bioactive compounds. Ursolic acid has a pentacyclic structure with low water solubility, which is a substantial bioavailability disadvantage. Several strategies, including the design of inclusion complexes between these acids and cyclodextrins, have been tried to increase solubility, biological potential, and bioavailability while maintaining physical and chemical stability, reducing toxicity, and representing an excellent prospect in clinical applications. Cosmetic composition can benefit from UA since it has antioxidant, antibacterial, and anti-irritant properties. Ursolic acid and/or its derivatives can be one of the active ingredients in a variety of cosmetics, such as anti-wrinkle creams and lip care cosmetics. UA was used in skin care emulsions for wrinkle treatment, moisturization and antiaging hydrogels, for lowering transepidermal water loss, in formulations for skin hydration and sedation, and in skin care preparations exhibiting an excellent percutaneous absorption promoting the action of an anti-inflammatory component. It also been used in preparations for treating and preventing skin roughness, as well as in cosmetics.

CONCLUSION

Ursolic acid is a pentacyclic triterpene that can be found in a variety of foods, medicinal herbs, and other plants. The fact that (3-hydroxy-12-urs-2-en-28-oic acid) is widely present in various plants means that it is frequently found in human diets. By combining with free acid or triterpenoid saponins to generate an aglycone, ursolic acid is transported throughout plants. The principal plants that contain ursolic acid include Malus pumila (apple), Ocimum basilicum (basil), Vaccimum spp. (blueberries), Vaccinium macrocarpon (cranberry), Ola europaea (olive), Origanum vulgare, Rosmarinus officinalis, Salvia, and Thyme (thyme). This family of natural isoprenoids has a wide range of biological actions, including antioxidant, antifungal, insecticidal, liver protecting, anti-inflammatory, anticancer, antiangiogenic, and proapoptotic

properties. Future studies should focus on improving the efficiency of extracting UA from new raw materials or wastes using more efficient and environmentally friendly methods, however the synthesis of UA derivatives could be a promising technology. UA is a natural product that has been used safely by humans in many forms as a component of ordinary fruits, herbs, and medicinal plants, as well as nutritional supplements. Anti-inflammatory and antioxidant pathways have been demonstrated in cell and animal studies, among the many pharmacological effects of UA. The CNS effect of UA has been demonstrated in chronic inflammation (arthritis, lung injury, sepsis, and colitis) models, in addition to its effects as an antidiabetic, antiobesity, antihyperlipidemic, hepato-, cardio-, and renoprotective agent and in chronic inflammation (arthritis, lung injury, sepsis, and colitis) models. In this communication, the terms "brain injury," "cerebral ischemia," "cognition deficit," "anxiety," and "depression" are used to assess the therapeutic potential of UA. The antioxidant and anti-inflammatory pathways are important for UA's effect, but there are additional mechanisms as well. Given the wide range of pharmacological effects and efficacy, a follow-up lead optimization investigation utilizing UA as a prototype drug candidate is warranted. These days, several nations use ursolic acid products often for disease prevention and/or therapy. Ursolic acid products are used, for instance, in China and Korea to cure cancer and protect the liver, as well as in Korea to treat rheumatoid arthritis and osteoarthritis, protect the stomach mucosa, and so on. Insulin metabolism and blood glucose levels are both controlled by it in certain cases. UA has the potential to improve the therapeutic efficacy of conventional medications in addition to its preventative properties. Through the inhibition of proliferation biomarkers (Ki-67) and microvessel density (CD31), activation of NF-B and STAT3, and expression of tumorigenic proteins regulated by these inflammatory transcription factors in tumour tissues, oral administration of UA (250 mg/kg) inhibited tumour growth and improved the antitumor effect of gemcitabine (25 mg/kg). The expression of miR-29a, which is closely associated with carcinogenesis, was also lowered by the combination of the two drugs in the tumour tissue. Evidence points to UA as a prospective candidate for use in the development of an all-encompassing competent strategy for the treatment and prevention of health issues. The review paper here discusses the potential medical benefits of UA.

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CHAPTER IV

DENDRIMERS AS A NEUROPROTECTIVE LEAD IN ALZHEIMER'S DISEASE: APPLICATIONS

ABSTRACT

Alzheimer's disease is a neurological ailment that is characterized by memory loss, cognitive decline and erratic behavior. Dendrimers, though, are a particular type of polymer that boasts a well-defined structure, high molecular homogeneity and low polydispersity, and can function as exceptional intracellular drug carriers with the potential to lower Alzheimer's disease symptoms. This chapter puts forth the idea of using dendrimers as therapeutic polymers in neurodegenerative therapy for Alzheimer's disease. The covalent bonding of ligands and append vectors is currently being explored in various targeting formulations. Clinical trial data, chemical bonding of dendrimers loading, and biological features can be utilized as nanoformulations for Alzheimer's disease treatment. Dendrimers in the lower range have an open structure, while dendrimers in the higher range have a more compact and spherical structure, making their handling more challenging. Dendrimers come in various sizes and shapes, resembling a range of biological structures, with a size and shape similar to hemoglobin (5.5 nm diameters). Dendrimers are produced through a stepwise repeating reaction approach, which involves radial synthesis from a central core. Each generation of dendrimer is characterized in terms of its size, shape, molecular weight, and number of surface functional groups, with progressive growth indicated by its generation number. The convergent approach was first reported by Hawker and Frechet. The present chapter focuses on the potential of dendrimers as drug transporters, and the data presented herein can be utilized for further research into dendrimer production and applications.

Keywords: Alzheimer, Dendrimers, Drug carriers, Drug loading, Generation, PAMAM

INTRODUCTION

Alzheimer's disease is a progressively degenerative neurological condition characterized by memory loss, disorientation, confusion, and other physical and psychological symptoms, as illustrated in Figures 4-1. The formation of intracellular neurofibrillary tangles, reactive microgliosis, astrogliosis, and the emergence of extracellular amyloid-beta deposits in senile plaques, represents the key histological hallmarks of AD. Primarily affecting the elderly, Alzheimer's disease leads to presynaptic and glutamatergic decline and is caused by a scientific prodrome. Lipophilic molecules, such as dendrimers, have demonstrated the ability to form covalent bonds with hydrophobic molecules, thus enabling them to cross the blood-brain barrier and function as additives. This polymeric dendritic presents a wide range of solubility options that can be modified and controlled through synthetic approaches to adjust their size, degree of branching, and functionality. These modifications can enhance their water solubility, reduce toxicity, increase permeability, protect them from enzyme destruction or hydrolysis, and/or improve site-specific drug delivery. Nanostructures are atom clusters that occupy space and range in size from 1 to 10 nanometers. Though dendritic structures have been around since 1978, the term "dendrimer" only emerged in the 1980s and carried with it negative connotations. These hyperbranched materials are considered a novel type of polymer with many intriguing properties. Dendrimers can be synthesized at the molecular level or through bottom-up methods and expand in size as furcated shells are rapidly produced. Treatments that have been conjugated or complexed to polymeric carriers (polymer therapeutics) have a longer half-life in circulation, a higher concentration (such as tumors or the reticuloendothelial system), and less non-specific toxicity. Polymer treatments can have a longer half-life in circulation, a higher concentration (such as in tumors or the reticuloendothelial system), and less non-specific

toxicity. Table **4-1** shows the results. The empty interior chambers and open conformations of dendrimers allow for the encapsulation of hydrophobic therapeutic compounds, enhancing their water solubility. Dendrimers have been discovered to be useful in the care of Alzheimer's disease, as well as in medicines, catalysis, and electronics. Cationic dendrimers have previously been shown to increase permeability. The cornea at physiological levels is negatively charged pH, this characteristic could be beneficial for an ocular medicine delivery system. This idea is supported by Vandamme and Brobeck.

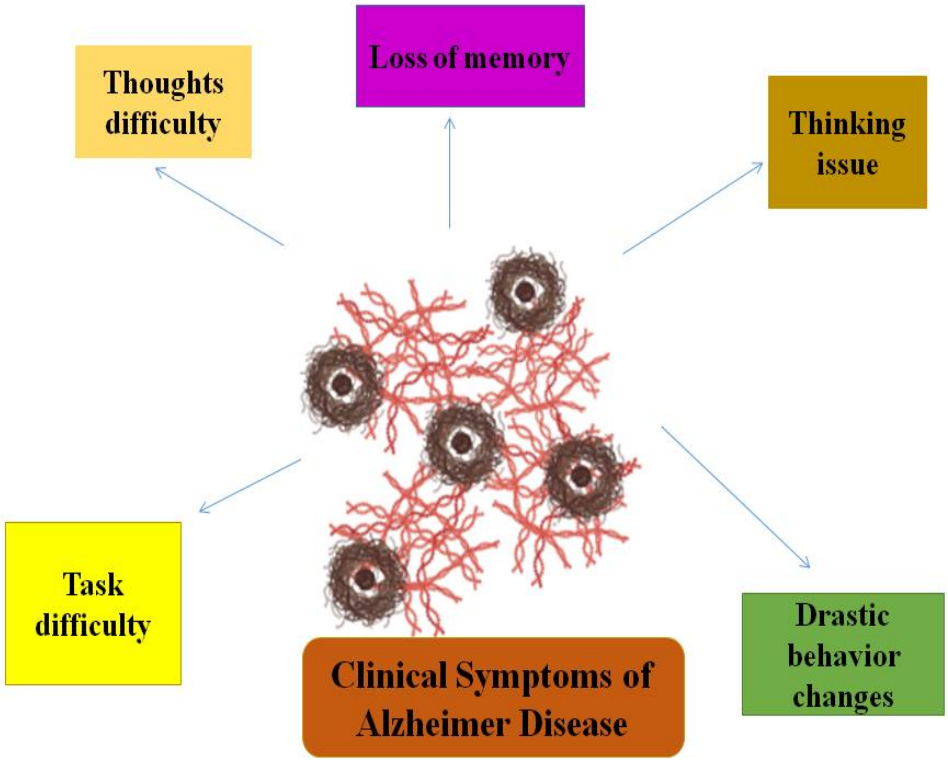

Figure 4-1: Clinical symptoms of Alzheimer's disease

Table 4-1: Description of dendritic polymers

S.No	Dendritic polymers	Description
1	Unimolecular micelles	Unimolecular micelles are dendrimers with an apolar core and polar shell. Newkome et al. reported the first such structure in 1985, which was an arborol. A symmetrical, four-directional saturated hydrocarbon cascade polymer with 36 carboxylic acid moieties and a neopentyl core was also synthesised by the same group. Lipophilic probes were found within the dendritic structures' lipophilic infrastructure, leading to the conclusion that the polymers exist as single molecules capable of molecular inclusion and so serve as unimolecular micelles. Hawker et al. described the synthesis of dendritic polyether unimolecular micelles with carboxylate surface groups using an electron-rich 3,5-dihydroxybenzyl alcohol building block.
2	PEGylated dendrimers	Dendrimers have been modified using poly (ethylene glycol) (PEG) in the development of solubilizing and drug delivery systems. PEG is usually conjugated to a dendrimer's surface

		to create a hydrophilic shell surrounding a hydrophobic dendritic core, resulting in a unimolecular micelle. Water-soluble dendritic unimolecular micelles were created by using 4; 4-bis (4V-hydroxyphenyl) pentanol building components and a PEG chain surface shell.
3	Dendritic box	The manufacture of dendritic boxes based on poly(propyleneimine) dendrimers. During the synthesis process, guest molecules may become trapped within the cavities of the dendritic boxes, with a dense surface shell inhibiting diffusion out of the structures, even after prolonged heating, solvent extraction, or sonication. A divergent strategy was used to make poly(- propyleneimine) dendrimers with primary amine end groups. The thick and rigid chiral shell4 with solid-phase properties and a flexible core capable of entrapping molecules was created by end group modification with a bulky amino acid derivative. 5 nm was determined to be the size of 5^{th} generation dendritic boxes.
4	Cored dendrimers	Zimmerman and colleagues created hollow nanosphere-like cored dendrimers and claimed that their ability to encapsulate substances made them viable for delivery vehicles. The interconnection of the dendritic wedges ensured structural stability after the core was removed. The core was removed by cleaving ester bonds, with the entire structure remaining unharmed due to sturdy ether connections. However, it is unclear how guest molecules might be loaded into such structures.
5	Dendrimer-based block copolymers	Several groups have synthesized dendrimeric di- and tri-block copolymers having linear hydrophilic block(s) and a hydrophobic dendritic block. Several of these systems have had their self-association of amphiphilic molecules in aqueous solution investigated, as well as the aggregates' ability to solubilize or combine weakly water-soluble compounds.

Dendrimer's Synthetic Aspects

Dendrimers are made by repeatedly adding Branching segments or monomers to each effective class in a central polyfunctional core, resulting in the upcoming generation of dendrimers with an increase in end groups for the remote response available in Figure **4-2**. For dendrimers, Tomalia and colleagues devised two basic synthetic approaches: divergent and convergent and lateral different miscellaneous approaches were identified as per Table 4-2.

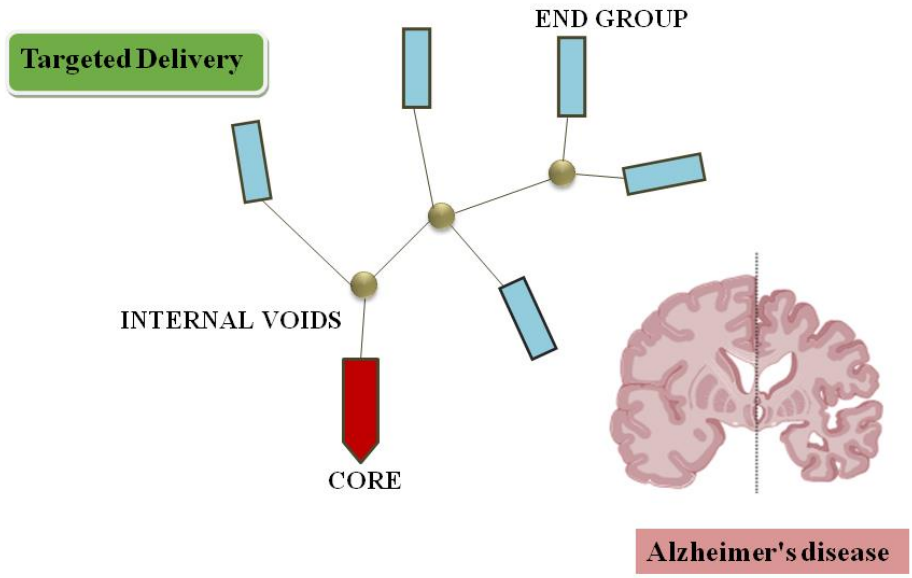

Figure 4-2: Structure of Dendrimer

Table 4-2: Different approaches used to obtain a functional dendrimers for drug loading

S.No	Approches	Description
1	Divergent Approach	The activation of functional surface groups is the initial stage in the divergent method, followed by the insertion of branching units.
2	Convergent Approach	The convergent approach has two steps: the first is recurrent coupling of protected or deprotected branches to generate a centre point functioned dendron, and the second is divergent interior fixing procedures, which results in multiple multidendron dendrimers.
3	Lego chemistry approach	Phosphorus-based dendrimers are created using "Lego" chemistry, which employs highly functionalized cores and branching monomers.
4	Click chemistry approach	Several writers reported using a Cu (I)-catalyzed reaction of 1, 2, 3-triazoles from azides and alkynes to create dendrimers with a variety of façade groups in high yield and purity using the "click" chemical technique.
5	Double exponential approach	The "double exponential" method allows monomers to be formed by divergent and convergent growth on a single substrate, and then the two products react to form an orthogonally protected trimer that can be used in a subsequent phase. The key benefit is quick synthesis, which can be used with either divergent or convergent approaches.

STRUCTURE, CHEMISTRY, AND GENERATION OF DENDRIMERS

Dendrimers are useful for biomedical applications and properties. The physicochemical properties of dendrimers are influenced by their synthesis, surface purpose, and divergent core structure. Dendrites solutions have a lower viscosity than linear polymers, which do not grow linearly with molecular weight but peak at the latest generation before declining. It arises as a result of form changes that have occurred over generations. Dendrimers in the upgraded generation forms and are closely packed because they have a hydrophobic core and a hydrophilic surface, they can solubilize hydrophobic compounds in watery conditions. Dendrimers as nanocarriers, including a lower susceptibility to reticulum endothelial absorption and they have a lower polydispersity index due to their highly controlled production. The outlying branches form spheres around a lower density core as branch density rises, resulting in greater peripheral density with the majority of the space remaining hollow in the core's direction. Drugs could be loaded in an empty spot. Dendrimers have several functional groups as shown in Table **4-3**, which can be used to attach vectors, devices, or ligands for targeting a specific location in the body. Dendrimers' neuropharmacological activity for Alzheimer's disease numerous studies have suggested that dendrimer systems are superior to other conventional nanocarriers in terms of drug loading, targeting, and physicochemical properties, so dendritic approaches have been investigated for drug delivery to improve drug concentration at the desired site of action and to protect the brain from oxidative damage. Dendrimers suppress aggregation and fibril formation, and they protect neurons from A-induced toxicity. Dendrimers can easily pass the blood-brain barrier due to their hydrophilic nature. Some ligand-based methods, such as transferring, have also been investigated for targeted drug delivery over BBB. Through several chemical processes, dendrons (branches of other atoms) sprout from this central structure. Dendrimer structure is still debated, especially whether they are fully stretched at the surface with maximal density. Dendrigrafts are a type of dendritic polymer, similar to dendrimers that may be made by monodisperse. The interior spaces of the dendrimer are filled with small substrates many years ago, both in hyperbranched polymers and dendrimers, and experimental evidence for unimolecular micelle characteristics was discovered. The poisonousness of G0 to G4 generations looks to be low, and they appear to be simple to handle. Divergent and convergent techniques are the two most common strategies for dendrimer synthesis. The new dendrimers created in consecutive generations had a molar mass that doubled with each group, culminating in a massive number of dendrimers. Hawker and Fréchet characterized synthesis as dendrimers with a multifunctional core that reacts with numerous dendrons, resulting in dendron fixation and a final hyperbranched product in the convergent approach. The key advantage of this technology is that dendrimers are easy to make, and the final reaction product is purified with accurate positioning Drug giants can be found covalently linked to functional groups on dendrimer surfaces or as non-covalent complexes with dendrimers of functional groupings on the outskirts and few flaws. These molecules have ammonia (NH3) or ethylenediamine ($C_2H_8N_2$) attach amine or amide to the core groups on the outside. Half-generation dendrimers are PAMAM dendrimers with terminal carboxylic groups. The dendrimer's molecular weight can be calculated quantitatively using an equation. PAMAM dendrimers were the first full family of dendrimers to be synthesized and commercialized, and they are one of the most studied. They were first described by Tomalia et al. in the 1980s. PAMAM dendrimers; diameters (D) range from 1 to 14 nm (or G0 to G10), as measured by transmission electron microscopes (TEM), differential scanning calorimetry (DLS), nano electrophoretic mobility molecular analysis (ES-GEMMA), as well as their radius of gyration (Rg) and zeta potential. The initiator core can be ethylenediamine (EDA), ammonia (NH3), or cystamine, with variable numbers of potential branches. PAMAM dendrimers have a geometry that is similar to that of micelles, and their accessible interiors could be exploited to encapsulate tiny guest molecules such as hydrophobic medicines. Low generation dendrimers (G5) have been observed to intercalate or adsorb to membrane surfaces, whereas high generation

dendrimers (G4) can trigger pore development and remove lipids from membranes. Electrostatic interactions between cationic or anionic terminated dendrimers and charged membrane lipids also influence these interactions, with charge-terminated dendrimers causing more membrane disruption than neutral dendrimers.

Table 4-3: Unique Properties of Denderimers

Core	Generation	Terminal group
EDA (Ethylene diamine)	4	Amine
DAB (Diainobutane)	4	Amidoethanol
DAH (Diaminohexane)	4	Succinamic acid
DAD (Diainododecane)	3.5	Sodium carboxylate
Cyst (Cystamine)	4	Tris (hydroxymethyl amino methane)

ADVANTAGES OF DENDRIMERS

1. Stability Enhancement.
2. Targeted Delivery.
3. Dummy and Carrier for Formulations Nanoparticles, Nano drugs.
4. Hydrogel for Ocular Drug Delivery.
5. Transdermal Drug Delivery.
6. Medical Applications (the drug delivery in the body which is directly related to the pharmacological therapy and also deals with diagnostic perspectives like gene therapy, cancerous drugs, magnetic resonance imaging contrast agents, etc).
7. Other Applications (Like in the field of cosmetics for controlled release of film-forming agents and also extend shelf life of the cosmetics product. L'Oreal Unilever and The Dow chemical company possess a patent for dendrimers in hair care, skincare, and nail care products).

POLYAMIDOAMINE DENDRIMERS

PAMAM dendrimers are a kind of pseudo macromolecule with distinct formation and framework that are highly branching and monodisperse. The divergent approach can be used for the synthesis of these nanocarriers. G0.5 generations can also be obtained by stopping the reaction sequence after adding methyl acrylate, which results in terminal carboxylate groups. Different functional groups, such as amino group (NH2), hydroxide (OH), aldehyde (CHO), methoxycarbonyl group (COOMe), di-tert-butyl dicarbonate (Boc), calcium oxide (COONa), and methyl group (CH3) group, could terminate PAMAM's superficial branches. PAMAM dendrimers can be changed to encapsulate pharmaceuticals or other cargos. Using this adaptable nanomaterial, it is feasible to control the interactions between PAMAM and the medication [14].

PAMAM DENDRIMERS AS SOLUBILITY ENHANCER

PAMAM dendrimers allow the improved water solubility and regulated release profile due to this molecular encapsulation. It's important to remember that noncovalent interactions including hydrogen bonding, electrostatic interactions, steric hindrance, and hydrophobic interactions can regulate the physical interactions between PAMAM and medicines in complexes in aqueous solution. The medication release profile may be affected by these interactions. The amine groups will be protonated, which will change their structure. Low pH can act as an adequate trigger for drug release. As a result, drug release from PAMAM dendrimers is pH-dependent and occurs more quickly in acidic settings. The most extensively used dendrimer is polyamidoamine (PAMAM), a collection of branched-chain dendrimers with polar solvents. The capacity of PAMAM dendrimer to increase the antifungal activity of clotrimazole against

different Candida strains was observed by Winnicka and colleagues. Jose and colleagues used different generations of PAMAM dendrimer (G1.0–G3.0) as agents in another investigation to improve the water solubility of amphotericin B, hence improving its antifungal activity.

ESTABLISHMENT OF PAMAM G4.0 DENDRIMERS

Using a diverging technique, PAMAM dendrimer generation 4.0 (PAMAM G4.0) was synthesized from the EDA core. The primary amine groups of EDA react with the acrylate groups of the MA in a Michael addition reaction to form half-generation PAMAM, which is followed by the reaction of the methyl propionate groups which is denoted by Gn.0. In a nutshell, EDA (20 mL) was mixed with 150 mL of methanol-dissolved MA. The reaction was stirred for 3 hours at 0°C and then for 48 hours at room temperature. A rotary vacuum evaporator (Strike 300, Lancashire, UK) was used to remove contaminants and solvents.

PROCESS OF DRUG LOADING

The drug was dissolved in a suitable solvent and formulated dendrimers in aqueous and both kept for 24 h and both were mixed with continued stirred then with the help of rotary evaporator the excess solved was removed. PAMAM dendrimer cavities have been loaded with a variety of chemotherapeutic drugs for the treatment of malignancies and disorders of various organs. Surprisingly, there are few examples of medications being loaded into PAMAM dendrimer cavities to treat brain illnesses. Swami and colleagues covalently bonded p-hydroxy benzoic acid to the surface of G4 PAMAM dendrimers with docetaxel (DTX), P-hydroxybenzoic acid (pHBA). The pHBA has a strong affinity for the sigma receptors found in the brain.

TARGETED NANOSCALE HIGHLY LIPOPHILIC PAMAM G4.0 DENDRIMER

The drug-loaded dendrimer or dendriplex must connect to cell membranes to pass through the blood-brain barrier or brain cells. Entry would be via receptor-mediated endocytosis if the dendrimer possesses a surface receptor. Adsorptive endocytosis will be used instead. The exact process by which the dendrimer enters a cell, particularly neurons and astrocytes, and releases its medication or gene is unknown. The following processes have been postulated for dendrimer uptake by cells: Endocytosis mediated by clathrin, caveolae (particularly for G4 dendrimers), and micropinocytosis. The biggest problem in brain delivery is figuring out the best way to distribute dendrimers to the central nervous system (CNS) while avoiding systemic toxicity. Injecting the dendrimer and its payload directly into the bloodstream is the simplest way to get a quick increase in blood concentration.

APPLICATIONS OF DENDRIMERS

Dendrimers are used in a variety of medical and practical applications nowadays those are enlisted below.

1. **Biomedical applications of dendrimers**

Dendritic polymers have potential applications in biomedicine. These dendritic polymers are functionalized in the same way as proteins, enzymes, and viruses are. Dendrimers and other molecules can be enclosed in their interior voids or connected to the perimeter. Polyamidoamine dendrimers, for example, are used in modern medicine as prospective blood substitutes. Dendritic polymers have potential applications in biomedicine. These dendritic polymers are functionalized in the same way as proteins, enzymes, and viruses are. Dendrimers and other molecules can be enclosed in their interior voids or connected to the perimeter. Polyamidoamine dendrimers are used in modern medicine as prospective blood substitutes.

2. **Anticancer drugs**

The ability of dendrimers to deliver novel drug delivery, in a sustained and controlled manner that is relevant to nanomedicine, is perhaps their most promising promise. Improved pharmacokinetic qualities of cancer medicines are one of the most fundamental concerns confronting modern medicine. Outflow, 'Enhanced penetration and retention' is the term for this

occurrence (EPR). Drug-dendrimer conjugates have a high solubility, low systemic toxicity, and selective accumulation in solid tumors. Various ways have been developed to contain medicinal compounds, genetic elements, and targeting agents within the dendrimer framework.

3. **Dendrimers in drug delivery**

For the first time in 1982, Maciejewski proposed the use of Upgrade molecules. Dendritic polymers' host-guest features are now being studied in the scientific community and have acquired prominence in the subject of working molecular chemistry. The process of a substrate molecule (guest) attaching to a receptor molecule is the basis of host-guest chemistry (host).

4. **Transdermal drug delivery**

For the first time in 1982, Maciejewski proposed the use of molecular carriers of these highly branched compounds. Dendritic polymers' main features are now being studied in the scientific community and have acquired prominence in supramolecular chemistry. The process of a substrate molecule (guest) attaching to a receptor molecule is the basis of host-guest chemistry (host).

5. **Gene transfer**

The primary assurance that understanding disease molecular pathways and sequencing the entire human genome would result in is that safer and more effective pharmaceuticals that will revolutionize how we treat patients are yet to be acknowledged. However, genetic therapies will likely add significantly to our therapeutic arsenal once some of the fundamental hurdles, such as focused and effective administration, are overcome. Transferring DNA fragments to the critical parts of a cell is tough. Dendrimers are now being studied to see if they can be used to carry genes into cells without causing DNA damage or deactivation. To maintain DNA activity during dehydration, the dendrimer/DNA complexes were encapsulated in a gel. A water-soluble polymer is coated on or sandwiched between two functional polymer films with a high breakdown rate to enable gene transfection. PAMAM dendrimer/DNA complexes were used to enclose functional biodegradable polymer films for substrate-mediated gene delivery using this method. In investigations, the fast-degrading functional polymer has shown to have a lot of potential for targeted transfection.

6. **Sensors on dendrites**

Despite being single molecules, dendrimers can have a large number of functional groups on their surfaces. This distinguishes them in applications requiring covalent bonding or intimate interaction between many species. The fluorescence of a fourth-generation poly (pro- pylene amine) dendrimer decorated with 32 dansyl units at the perimeter was investigated by Balzani and associates. The inside of 30 aliphatic amine units makes up the dendrimer, allowing appropriate metal ions to coordinate. When a Co2+ ion is introduced into the dendrimer, the intense fluorescence of all the dansyl units is quenched as was discovered.

7. **Photodynamic treatment**

The use of visible or near-infrared (NIR) light to activate a cell is known as photodynamic therapy (PDT). Photosensitizing agent excitation generates a high energy state that, when combined with oxygen, produces singlet oxygen that is highly reactive and can cause necrosis and death in tumor cells. Dendritic injection of PDT medicines has become popular in recent years. Studied was an attempt to increase tumor selectivity, retention, and pharmacokinetics.

CONCLUSION

Dendrimers possess unique features that render them appealing options for diverse applications. They are synthetic macromolecules consisting of an extensive molecular structure and numerous well-defined functional groups. Since the advent of the first dendrimers, dendrimer chemistry has surged in popularity. Dendrimers offer the potential to fabricate well-defined nanocarriers for cell transportation. The surface engineering of dendrimers facilitates fine-

tuning of their function and characteristics, which can be tailored to meet the specific requirements of individual applications. Additionally, dendrimer carriers can traverse biological barriers, such as the gastrointestinal tract and the blood-brain barrier, which is gaining more recognition. Future research endeavors in this field will also hinge on the fabrication of biocompatible dendrimers.

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CHAPTER V

MEVALONATE PATHWAY: A PROMISING AVENUE FOR THE TREATMENT OF ALZHEIMER'S DISEASE

ABSTRACT

The mevalonate pathway plays a crucial role in the synthesis of cholesterol and various non-sterol isoprenoids in the brain. This pathway is responsible for the conversion of acetyl-CoA into a range of sterol and non-sterol compounds through a series of enzyme-mediated processes. The resulting products include farnesylpyrophosphate (FPP), geranylgeranylpyrophosphate (GGPP), ubiquinone, and dolichol. The mevalonate pathway, along with the 1-deoxy-D-xylulose-5-phosphate (DXP) pathway, is utilized by nature to produce isoprenoids. Disruptions in the mevalonate pathway enzymes can lead to structural abnormalities in the brain and may be accompanied by neurodevelopmental and behavioral issues. The initial route for the production of isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) is the mevalonate pathway. It involves a series of six enzymatic steps that convert acetyl-CoA into IPP. The enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) converts acetoacetyl-CoA into mevalonate, which is further processed to generate non-sterol isoprenoids such as dolichol, heme-A, isopentenyl tRNA, and ubiquinone, as well as sterol isoprenoids like cholesterol. In Alzheimer's disease (AD), the lipid products of the mevalonate pathway are believed to be tightly regulated through post-translational modifications of the enzymes or alterations in substrate levels. While recent studies have started exploring the role of non-sterol isoprenoids in the mevalonate pathway, the majority of research in AD has primarily focused on cholesterol. Cholesterol homeostasis has been shown to play a critical role in controlling the synthesis of amyloid-beta (Aβ), the formation of amyloid plaques, tau hyperphosphorylation, Aβ toxicity, and other pathological mechanisms associated with AD. This review study aims to emphasize and elucidate the significance of the mevalonate pathway in AD. There is substantial evidence suggesting that alterations in cholesterol metabolism and homeostasis have profound implications for the pathogenesis of AD. Dysregulation of cholesterol synthesis and metabolism can contribute to the accumulation of Aβ peptides and the subsequent formation of amyloid plaques in the brain. Moreover, disrupted cholesterol homeostasis can impact tau protein phosphorylation, leading to the development of neurofibrillary tangles, another hallmark of AD. Understanding the intricate interplay between the mevalonate pathway, cholesterol metabolism, and AD pathology is crucial for identifying novel therapeutic targets. By targeting key enzymes or regulatory mechanisms within the mevalonate pathway, it may be possible to modulate cholesterol levels and restore lipid homeostasis, thereby potentially mitigating the progression of AD. Additionally, exploring the roles of non-sterol isoprenoids in AD pathogenesis warrants further investigation. In this chapter, the mevalonate pathway plays a pivotal role in cholesterol and non-sterol isoprenoid synthesis in the brain. Dysregulation of this pathway, particularly in cholesterol metabolism, is implicated in the pathogenesis of AD. Elucidating the molecular mechanisms underlying the connection between the mevalonate pathway and AD pathology may provide valuable insights for the development of effective therapeutic interventions to combat this devastating neurodegenerative disease.

Keywords: Neurofibrillary tangles, Mevalonate Pathway, Alzheimer's disease, Amyloid plaques, AD pathology

INTRODUCTION

The balance between cholesterol synthesis, uptake, efflux, and metabolism is known as cholesterol homeostasis. In the brain, this process takes on peculiar characteristics due to

differences in how well neurons and glia can carry out each of these processes. While local cholesterol synthesis declines with age, the brain is capable of producing sufficient cholesterol to meet its demands during development and adulthood. The importance of endogenous cholesterol synthesis for proper brain function is underscored by the fact that genetic deficiencies in cholesterol synthesis enzymes can lead to severe neurological disorders [1]. The mevalonate pathway is primarily responsible for de novo production of brain cholesterol. This pathway involves the conversion of two molecules of Acetyl-CoA, produced in the citric acid cycle, into one molecule of IPP through a series of six enzymatic steps [2]. The mevalonate pathway, which occurs in the cytosol, and the plastid-localized DXP pathway are the two separate pathways involved in the synthesis of the basic C5 unit [3]. Prenyltransferases, such as GPP and GGPP synthases, have also evolved from an endosymbiotic origin and catalyze the union of the C5 units to generate acyclic prenyl diphosphates [4]. In the brain, cholesterol production is robust to address its specific needs. Cholesterol plays critical roles in axonal development, neurotransmitter release, neurosteroid generation, and synaptogenesis [5].

While astrocytes, which support the formation and maintenance of axons, dendrites, and synapses, produce cholesterol at a lower rate compared to neurons, they are still important contributors. It has been hypothesized that neurons do not require autonomous cholesterol synthesis and make minor contributions to adult brain cholesterol synthesis. This hypothesis is based on the finding that suppressing cholesterol synthesis in adult cerebellar neurons did not affect their viability or the shape and density of synapses [6]. One crucial enzyme involved in cholesterol metabolism in the brain is cholesterol 24-hydroxylase (CYP46A). It converts excess cholesterol in neurons into 24(S)-hydroxycholesterol (24-HC), a more polar metabolite that can cross the blood-brain barrier. CYP46A1 is partially expressed in specific brain regions, such as Purkinje cells in the cerebellum and pyramidal neurons of the hippocampus and cortex, but not in astrocytes. The regulation of the mevalonate pathway is influenced by 24-HC, which acts as a crucial regulator [7]. In astrocytes, 24-HC also controls cholesterol efflux. Additionally, cholesterol can be esterified through the action of the enzyme acyl CoA-cholesterol acyltransferase (ACAT) [8]. Although cholesterol esterification is not a significant metabolic activity in the brain, with cholesterol esters comprising only 1% of the total cholesterol content in the brains of humans and mice, ACAT has been identified as a critical enzyme in AD [9]. Many of the genes associated with cholesterol in AD encode substances involved in the glia/neuron cholesterol shuttle processes, including apoE, apolipoprotein clusterin, ABCA1, CYP46A1, various LDL receptors, and ACAT. However, when it comes to the genetic relationship between AD and the enzymes involved in the mevalonate pathway, there is currently less evidence available [10].

The Mevalonate Pathway in AD

The mevalonate pathway is the only one used by the brain to create cholesterol and other non-sterol isoprenoids, including farnesylpyrophosphate (FPP), geranylgeranylpyrophosphate (GGPP), ubiquinone, and dolichol. Acetyl-CoA is converted into various final sterol and non-sterol compounds via a series of enzyme events in the mevalonate pathway [11]. The mevalonate route into the following parts for discussion purposes the shunt pathway, the non-sterol isoprenoids pathway, the post-squalene pathway, and the pre-squalene pathway (figure 1) [12]. Numerous studies have been conducted on the kinetics of the enzymes involved in the mevalonate pathway [13]. The mevalonate pathway's enzymes are expressed in the brains of rats and humans, and many of them have their expression controlled by developmental factors in the brain. Neurodevelopmental and behavioural problems may coexist with anatomical abnormalities of the brain caused by inborn errors in mevalonate pathway enzymes [14]. Despite certain exceptions, there is little evidence about changes in the lipid intermediates and enzymes of the mevalonate pathway in AD brains as shown in Figure 5-1 [15]. It appears that the mevalonate pathway's lipid products are highly individually regulated in AD, most likely as

a result of post-translational alterations to the enzymes and/or variations in substrate concentrations [16]. Although more recent research has also focused on the non-sterol isoprenoid branch of the mevalonate pathway, most investigations on the system's role in AD have concentrated on cholesterol [17]. Even though there is substantial evidence suggesting that changes in plasma cholesterol levels may be significant to the formation and/or progression of AD. With news that patients on statins had a lower prevalence of AD than the general population, interest in understanding the involvement of the mevalonate pathway in AD grew [18]. To prevent cholesterol buildup and to provide a sufficient supply of non-sterol isoprenoids, the mevalonate pathway is strictly regulated at the transcriptional and post-transcriptional stages. The importance of the dysregulation of cholesterol homeostasis in AD is highlighted by the discovery that several genes involved in cholesterol homeostasis represent susceptibility loci for sporadic or late-onset AD and the evidence that alterations in cholesterol homeostasis are significant in the regulation of formation of amyloid plaques, tau hyperphosphorylation, Aβ toxicity, and other mechanisms [19]. Disturbances in cholesterol homeostasis in AD could be pathogenesis-related as well as a result of the neurodegenerative process [20].

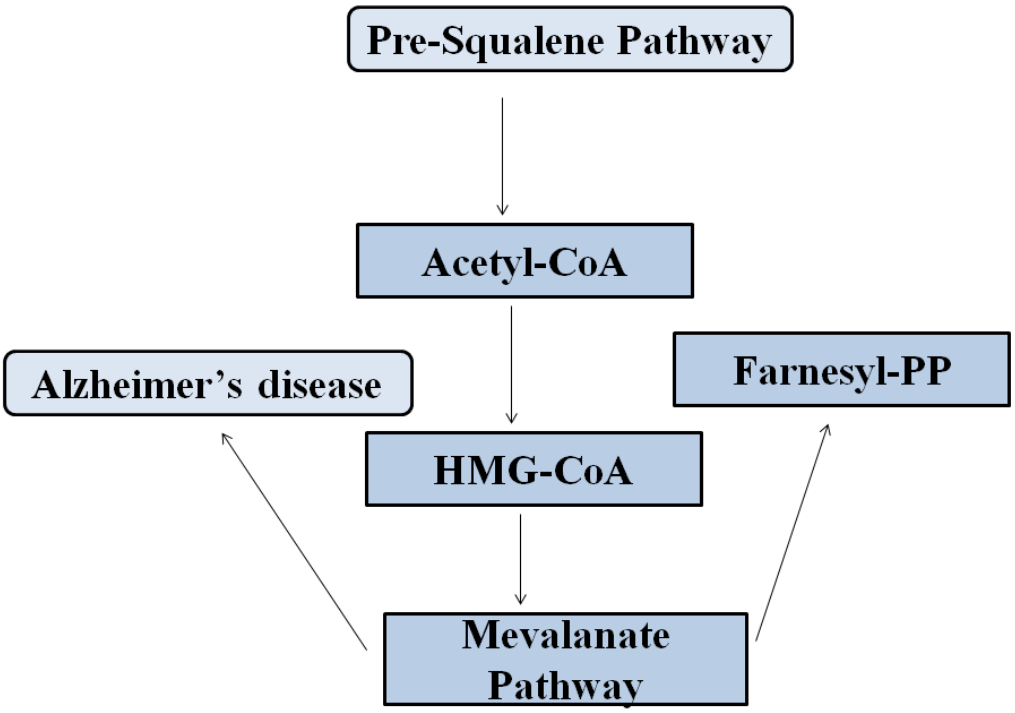

Figure 5-1: The Mevalonate Pathway

Mevalonate Pathway

MVA (Mevalonate) route, often referred to as isoprenoid or the 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) pathway, is an anabolic pathway that metabolites for a variety of cellular processes in eukaryotes, archaea, and some bacteria. Isoprenoids, a varied family of approximately 30,000 biomolecules including cholesterol, vitamin K, coenzyme Q10, and all steroid hormones, are made from two five-carbon building blocks named isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP), which are produced by the process [21-25]. Seven enzymes are thought to make up the mevalonate pathway: acetoacetyl-CoA thiolase, HMG-CoA synthase, HMGR, mevalonate kinase, phosphomevalonate kinase, diphosphomevalonate decarboxylase, and IPP isomerase. Thioester-dependent Claisen

condensation process between two molecules of acetyl-CoA is the first step in the mevalonate pathway, and it is catalysed by acetoacetyl-CoA thiolase (EC 2.3.1.9), which produces acetoacetyl-CoA [26-27]. The six-carbon complex (3S)-HMG-CoA is subsequently produced through a second condensation process with a third acetyl-CoA molecule. HMG-CoA synthase catalyses the condensation reaction, an aldol-like mechanism (EC 2.3.3.10) [28]. The rate-limiting enzyme of the mevalonate pathway, HMGR (EC 1.1.1.34), then reduces HMG-CoA to mevalonate. Sterols and isoprenoids, which have been proven to be essential for tumour growth, are produced through the mevalonate pathway. The growth and survival of several types of cancer cells depend on a number of enzymes in this pathway [29]. HMG-CoA reductase (HMGCR) converts 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) to mevalonic acid (mevalonate), which is the first committed step of the mevalonate pathway. Mevalonate is converted into isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate in the subsequent phase of the route (DMAPP). Geranylgeranyl pyrophosphate synthase catalyses still another condensation reaction to produce geranylgeranyl pyrophosphate, which is produced by the consecutive condensation reactions of DMAPP with two units of IPP (GGPP). The branch point for numerous routes leading to different end products, such as cholesterol, steroids, and dolichols, is the FPP. In addition, GGPP synthase can transform FPP into geranylgeranyl pyrophosphate (GGPP). Squalene synthase plays a critical function in directing intermediates to either sterol or non-sterol branches of this metabolic pathway. It catalyses the first step in the route that is dedicated exclusively to cholesterol production. Investigations have also been made on the mevalonate pathway's oncogenic potential. It has been demonstrated that the mevalonate pathway promotes proliferation in primary leukaemia cells. A common biosynthetic intermediary of isoprenoids called mevalonate is used in biochemical studies as well as as a moisturiser in cosmetics. The blood brain barrier (BBB), which is normally impermeable to plasma lipoproteins, separates the brain from the peripheral pool of cholesterol, making cholesterol production in the brain essential. As a result, the mevalonate pathway is virtually entirely where de novo manufacture of brain cholesterol occurs. To address the needs of the brain, in-brain cholesterol production is quite vigorous. In addition to playing critical roles in axonal development, neurotransmitter release, and the generation of neurosteroid, cholesterol is necessary for appropriate synaptogenesis. The mevalonate route is the only one used by the brain to synthesise cholesterol as well as other non-sterol isoprenoids, including dolichol, ubiquinone, and farnesylpyrophosphate (FPP), geranylgeranylpyrophosphate (GGPP), and geranylgeranylpyrophosphate (FPP). Acetyl-CoA is transformed into various final sterol and non-sterol compounds via the mevalonate pathway, which consists of several enzyme steps. Several members of the LDL receptor family, ACAT, apoE, the apolipoprotein clusterin, ABCA1, CYP46A1, and other cholesterol-related genes have been linked to AD. These genes predominantly encode components of the glia/neuron cholesterol shuttle activities. Regarding the genetic link between AD and the genes for the mevalonate pathway's enzymes, far less information is available. The enzyme cholesterol 24-hydroxylase (CYP46A1) helps neurons convert extra cholesterol into (S) hydroxycholesterol (24-HC), a more polar metabolite that can traverse the BBB. Only Purkinje cells in the cerebellum and pyramidal neurons of the hippocampus and cortex produce CYP46A1, which is not present in astrocytes. A crucial regulator of the mevalonate pathway is 24-HC. In astrocytes, 24-HC also controls cholesterol efflux. The enzyme acyl CoA-cholesterol acyltransferase (ACAT) catalyses the esterification of cholesterol as well [30]. ACAT has been discovered as a key enzyme in AD despite the fact that cholesterol esterification is not a significant metabolic process in the brain and cholesterol esters make up only 1% of the total amount of cholesterol in mouse and human brains. The conversion of 1-deoxy-d-xylulose 5-phosphate (DXP) into 2-C-methyl-d-erythritol 4-phosphate is catalysed by the enzyme 1-deoxyxylulose 5-phosphate reductoisomerase (DXR, EC 1.1.1.267). (MEP). This transition occurs in two steps: first, DXP is rearranged to generate the probable intermediate 2-C-methyl-d-erythrose 4-phosphate, and then the later aldehyde is reduced in a

NADPH-dependent manner. It was demonstrated that the rearrangement of DXP into [5-(13)C]2-C-methyl-d-erythrose 4-phosphate, which does not require an areduction step, is NADPH dependent when [1-(13)C]DXP was used as a substrate. The putative aldehyde intermediate, produced through chemical synthesis, was changed into MEP and DXP by the DXR in the presence of NADPH and NADP(+), respectively. This proves that the DXR is capable of catalysing reversible reactions. The transformation of MEP into DXP in the presence of NADP(+) provided more evidence of its reversibility. The transformation of MEP into DXP in the presence of NADP(+) provided more evidence of its reversibility.

Deoxyxylulose/Methylerythritiol Phosphate (DXP) Pathway

The creation of methylerythritol phosphate by reductoisomerase IspC is the first committed step in the biosynthesis of non-mammalian isoprenoids. DXP synthase catalyses a thiamine diphosphate (ThDP)-dependent activity in which pyruvate and d-glyceraldehyde 3-phosphate (d-GAP), the natural substrate for this reaction, are converted into 1-deoxy-d-xylulose 5-phosphate (DXP). This initial stage, which denotes a branch point in bacterial metabolism, is thought to be rate-limiting in some organisms. DXP synthase is a possible target for the development of anti-infective drugs due to its crucial function in pathogen metabolism and its probable regulatory role in isoprenoid production. DXP synthase catalyses a process that combines aspects of the chemistry of carboligase and ThDP-dependent decarboxylase, and the active site residues required for coordinating the cofactor are conserved in comparison to other ThDP-dependent enzymes. Pyruvate is decarboxylated by DXP synthase, which then catalyses the condensation of the hydroxyethyl-ThDP intermediate with d-GAP. This process is related to acetolactate synthase, glyoxylate carboligase, and transketolase, whose acceptor substrate is also an aldehyde. These enzymes use similar decarboxylation and carboligation chemistry to produce acetohydroxyacid and tartronate semialdehyde, respectively. Interestingly, compared to other ThDP-dependent enzymes, DXP synthase has several distinct structural characteristics [30].

CONCLUSION

In Alzheimer's disease (AD), deregulation of the mevalonate pathway can impact both neurons and glia in several ways. Our research suggests that cells involved in Aβ accumulation, likely neurons, may specifically experience inhibition of the mevalonate pathway. The extent to which this inhibition affects the overall concentration of cholesterol and isoprenoids in the brain depends on the proportion of cells harboring intracellular Aβ. It is possible that the synthesis of cholesterol by astrocytes compensates for the reduced cholesterol synthesis in neurons. Dysregulation of the mevalonate pathway in AD affects cholesterol, a sterol, and isoprenoids, a class of non-sterol compounds. At the subcellular level, there is a reciprocal regulation between cholesterol and Aβ.

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CHAPTER VI

GREEN SYNTHESIS OF SILVER NANOPARTICLES USED BIOMEDICAL APPLICATION

ABSTRACT

In the current scenario, silver nanoparticles (AgNPs) are of critical interest. Nanotechnology has explored a number of intriguing ways in the field of molecular material sciences. The use of the Spartium junceum flower extract as a reduction, stabilization, and defining characteristics of and assessment parameters of an aqueous silver nitrate solution as an environmentally friendly, quick approach to silver nanoparticle synthesis (AgNPs). The parameters of the process, such as pH, temperature, plant extract content, and reaction time, were examined to improve the biosynthesis of silver nanoparticles. The antimicrobial, antibacterial, and antifungal characteristics of silver nano range particles make them a promising technique for drug delivery. In the nineteenth century, the idea of nanotechnology was initially presented. The nanoscale spectrum was discovered by R. Feynman. The green production of AgNPs using Hibiscus cannabinus leaf extract showed significant antimicrobial action against E. coli, P. mirabilis, and Shigella flexneri. AgNPs have been shown to exhibit anti-inflammatory, anti-fungal, anti-angiogenesis, anti-viral, and anti-platelet activity in addition to being an essential antibacterial agent against a variety of pathogenic microbes. The disc diffusion method was used to test bacterial antibiotic sensitivity. The release of diffusible inhibitory chemicals from silver nanoparticles inhibited bacterial growth across the well. Bigger particles would have a better bactericidal effect than smaller particles with a larger contact region. UV-Visible Spectroscopy and Transmission Electron Microscopy were used to characterise the Silver Synthesized Nanoparticles (TEM). The scale was judged to be 18 nm. A qualitative assessment of the leaf extract reduction capacity was also carried out, indicating that considerable.

Keywords: Silver Nanoparticle, Nanotechnology, Anti-inflammation, Material Sciences, UV-Visible Spectroscopy, Transmission Electron Microscopy

INTRODUCTION

Nanoparticles were created in 1960 with the intention of being used for clinical, medicinal, and vaccine purposes and they have since changed the medical landscape. The Rudimentary, titled "An approach to the creation of general capabilities for molecular manipulation" was introduced in 19 century. The word nanotechnology was first used in the vast field of science in 1974 by Nario Taniguchi's paper "Nanotechnology". Professor P. P. Speiser and his team explore the use of polyacrylic beads for micro-matrix goal. Nanoparticles were created in 1960 with the intention of being used for clinical, medicinal, and vaccine purposes and they have since changed the medical landscape. The Rudimentary, titled "An approach to the creation of general capabilities for molecular manipulation" was introduced in 19 century. The word nanotechnology was first used in the vast field of science in 1974 by Nario Taniguchi's paper "Nanotechnology". The processing, separation, and aggregation of materials, as well as their deformation by one or more molecules of atomic or molecular weight, are the key topics of the research paper. Nanotechnology is a relatively new and rapidly emerging specialization in researches that scale up the range of vital interest and benchmark connecting manmade and botanical structure. Partition, fusion, and subject matter squinting by a unique granule are the three methods most commonly used in nanotechnology.

Wet nanotechnology: The enzymes, membranes, and cells of the biological system were all harmed as a result of this.

Dry nanotechnology: Surface science and physical chemistry are significant, and carbon, silicon, and inorganic materials structure manufacturing receive special attention.

Computational nanotechnology: the stimulates the complex nano-scale structure due to their peculiar opto-electron and physicochemical properties, metal nanoparticles, which are used in a variety of fields such as molecular diagnostics and opioid abuse, imagers, catalysts, and sense, have piqued scientists' interest. As a consequence, in nanoscale technology research the most efficient, environmentally friendly, and cost-effective.

Due to a need to limit or remove the use of environmentally dangerous substances as described in Green chemicals, the nanoparticles synthesised in the last decade receives great attention. Both live organisms, including bacteria, fungi and plants, are necessary for biosynthesis. The plants were used in lively organisms primarily because the plants' synthesis is safer, more environmentally friendly, cheaper and simpler than microbial synthesis.

Nanoparticles are now successfully synthesized with these systems.

SILVER NANOPARTICLES

Silvery, also called Raupya and Chandi Bhasma, by ancient people which labelled that boosts immune response. Silver nanoparticles (AgNPs) are the finest noble metals in nanoparticles, where their wide surface area offers effective antimicrobial action. Silver nanoparticles have a number of useful uses in medicine, such as antibacterial properties, anti-malarial, antifungal, larvicidal, anti-plasmodial, against cancer, against acne, against wounds often used in first aid devices such as PMMA, incision instruments, and incision masks and activator operation. By following the M4 ICH guidelines, AgNPs are frequently used in the textiles industry, as well as for domestic water purification, cosmeceuticals, and medical devices. As per Figure1, AgNPs have pleasant optical properties, making them ideal for biosensing and photography. Silver nanoparticles are used in adhesives, conductive inks, and pastes, as well as a wide variety of electronic devices, due to their peak conductivity. Furthermore, AgNPs serve as catalysts in a variety of chemical reactions, including styrene oxidation. AgNPs have a plethora of applications in drug delivery ointments, chemical sensing, nanomedicine, data storage, food industry, textile photocatalytic organic colour degradation, anti-oxidation and antimicrobial agents have contributed significantly.

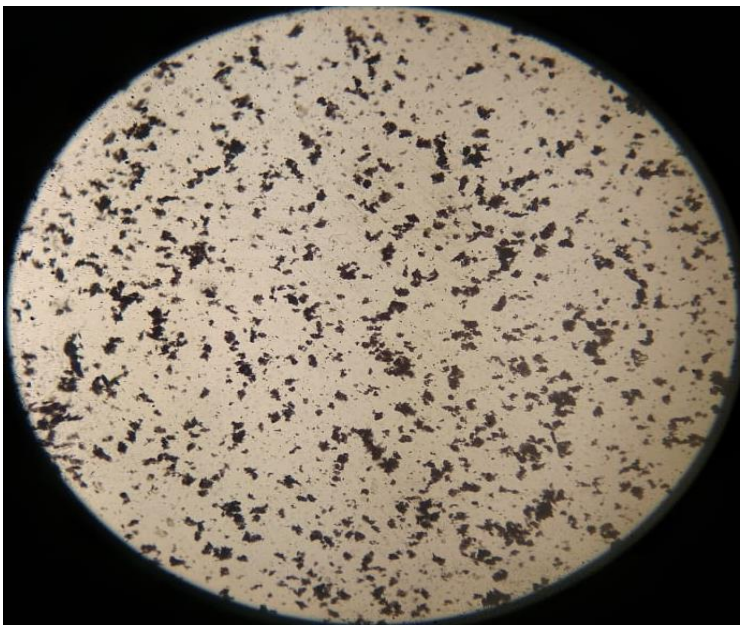

Figure 6-1: Silver Nanoparticles

SYNTHESIS OF SILVER NANOPARTICLES

Nanoparticles were prepared using three separate techniques for this crucial step:

1) An approach that is physical as Physical approach

2) Use chemistry as Chemical Approach

3) An approach based on biology as Biological approach

Physical & Chemical Approaches

Nanoparticles were freshly formulated using a furnace-tube at atm. and evaporation or condensation. This strategy is under pressure. For the synthesis of AgNPs, specialised physical techniques such as spark discharge and pyrolysis were used. Physical methods include benefits such as the use of radiation and temperature as mitigating agents, as well as the removal of toxic chemicals, but drawbacks include higher energy consumption, low yield, solvent toxicity, and the lack of uniform delivery. Water or organic solvents were needed in chemical approaches for the fabrication of silver nanoparticles. Usually, three main ingredients are required for this procedure: precursor metals, reducers and stabilizers/caping. The aim is mainly to reduce silver salts in 2 (1) nucleation stage and (2) gradual evolution. In general, there are two methods for making silver nanomaterials: "top-down" and "bottom-up". Mechanical scrubbing was used to scrub large metals, followed by colloidal protective materials for subsequent stabilisation, in the top-down process. The "bottom-up" methods were chemical reduction, electrical chemistry, and sono-decomposition. Chemical approaches are more clearly defined than physical approaches, which is a distinct advantage of this method. These techniques were incredibly costly. Furthermore, toxic and hazardous agents were used to make AgNPs, such as 2-mercaptoethanol, borohydride, citrate, and thio-glycerol. Aside from these disadvantages, the sensitive shaped particles were not expected to be washed because their surfaces had been chemically sedimented. AgNPs of well-defined nano- sizes explain the baffling nano-sizes restriction that was baffling to plan, as well as the required step to prevent particle aggregation. Furthermore, various dangerous and lethal derivatives are removed at the time of procedure. Atomic methods necessitated step like in fusion method, Lithography, photo ablation, Laser irradiance, Chemical decomposition electrochemical lesser, Sono-decomposition, Thermal decomposition, Electrochemical lessen.

Green Chemistry Approach

Biotic methods involved emerged and feasible solutions for overcoming chemical process limitations. Recently, biomedicable nanoparticles have demonstrated fast, inexpensive, effective, and environmentally safe approaches, with a focus on high-yield production of specified-size AgNPs using a variety of bio-materials, such as herbal extracts, mushroom related bodies, and small living bit like specified amino acids and qualitative vitamins. Nanoparticle synthesis through bio-sorption of metals was discovered in Gram-negative and Gram-positive bacteria. In the absence of biologically toxic chemicals, several studies have shown that AgNPs can be synthesised using natural, economical, and biologically compatible methods. P. stutzeri AG259 was given green chemical treatments, *B. licheniformis*, *L. strains*, *Brevi-bacterium*, *E. coli*, Together with *Fusarium oxysporum*, the fungus, and *Ganoderma neo-japonicum Imazeki* in this manner Biopolymers, for example, are a type of biomolecule, amino acids& enzymes were also utilized, starch. The solvent, reducing agent, and non-toxic substances all affect nano-particular biosynthesis in different ways. The key advantage of a biological approach is the ease with which protein, secondary metabolites, or amino acids can be accessed during the synthesis process. The removal and use of bio-molecules for AgNPs synthesis, as well as the additional steps needed to prevent particle aggregation, are both environmentally friendly and non-polluting. Biological methods tend to provide controlled particle size and shape, which is important in biological applications. Biosynthesis produces particles of a specific size and

shape, which is important for a variety of biomedical applications. Biological approaches also benefit from access to a variety of ecological resources, reduced time consumption, stability and water-based nanoparticles that are easily soluble. The biological activity of AgNPs is determined by the particle's structure, morphology, and scale. Smaller, three-part truncated nanoparticles are more favoured and effective in terms of size and shape. Several studies have successfully synthesised AgNPs of different shapes and dimensions, but there are still some limitations. The specified preparation of silver-colloids for controlled the shape and size of internal surface with a vast substance of reducing proxy, like NaBH4 were considered. Mechanical operation, such as temperature precursor numbers, stabilisation factors, pH and reduction, can all is improved. In comparison to chemicals, biotic methods construct it calm to control form, measurements of the formulated silver nano range particles.

Characteristics of silver nanoparticles

For their nature, biodiversity, purity and efficacy, the physical properties of nanoparticles are important. Therefore, the characterisation of AgNPs is essential for the evaluation of functional criteria for nanoparticles. Silver nanoparticles feature a variety of analytical technology features, including UV spectroscopy, Fourier Transform, Electron Microscopy, Atomic Force Spectroscopy, XRD and X-ray (XLS) spectroscopy. Silver nanoparticles have been used for the purposes of the scanning and scanning of silver nanoparticles. Several competent publications and reviews addressed different types of analysis for AgNPs characterization and used these principles, but for the purposes of interpreting skill, the outlines of the essential techniques for characterising AgNPs are given below.

Ultraviolet-visible Spectroscopy

The use of this method to characterise and track the synthesis and stability of AgNPs in synthesised nanoparticles is a very convenient and efficient process. Because of their optical properties, AgNPs interacted strongly with various light wavelengths Furthermore, for many NP types, ultraviolet-visible spectroscopy is less complex, sensitive, and understandable. For the characterisation of colloidal suspension particles, very little measuring time is required, and no calibration is required. AgNPs' drive and valence ribbons are very close to each other, allowing electrons to freely pass between them. Oscillation of conduction resonant is occurring due to movement of electrons at specific wavelength. The absorption of AgNPs is influenced by different factors. This timbre is famous for its diverse metal nano-particles in the dimensions of 2-100nm. A plasma surfactant has been treated with this pitch. The biological stability of AgNPs has been identified. These methods have been published for over a year, and UV-visible spectroscopy revealed an SPR peak at the exact frequency.

X-ray Diffraction (XRD)

This characterization is used in the investigation of molecular and crystal structures, of a particular compound is examined degree of crystallinity measurement, chemical resolutions, particle size, Isomorph substitutes, etc. Various diffraction patterns are a representation of the physicochemical features.

The atomic-scale crystalline structure detection technique XRD is widely used. With a promising method for both organic and inorganic crystalline materials was evaluated. This particular electric device was used for stage identification, and structural disfigurement verification of specimen from various sources, including, environment. The application of XRD to the characterization of an extensive range of nanomaterials and their values has recently expanded.

Fourier Transform Infra-red (FTIR) Spectroscopy

The benefits of FT-IR include fidelity, precision, and a constructive wave-to-sound ratio. FT-IR enables differential spectroscopy to differentiate subtle functionally active residue absorbent

bands from large background protein absorption, allowing for tiny differences in absorption in the range of 10 to 3nm. This process is commonly used in educational and trade research, as well as in the combination of nanoparticles, to assess if biomolecules are more prominent. This technology has been applied to aware of nano-sized materials, such as justification on silver, graphene, gold nanoparticles, and carbon nanotubes, covalently greased functional molecules, and substrate-enzyme interaction during catalytic cycle. For a non-invasive procedure, fact this spectrometer's advantages include fast performance, decent signal, high signal-to-noise ratios, and less specimen heating. FTIR spectroscopy, a relatively modern method, has recently made considerable progress. For NPs, FTIR Spectroscopy was a common and novel process. As a result, FTIR is a suitable, useful, painless, inexpensive, and simple method of determining biomolecules' position in the silver nitrate reduction process.

Scanning Electron Microscopy

The high-tech creation of nanomaterials range and a powerful electron beam to enable researchers to learn about structures on an extremely fine scale. SEM provides a Surface imaging technique capable of resolving a wide range of synthesised micro- and nanoparticles. Manually measure and count particles using SEM and we can quantify and extract the histogram from photographs using special software. Silver powder can be examined and analysed using a combination of power dispersive X-ray spectroscopy and scanning electron microscopy. SEM has the disadvantage of no longer being able to resolve internal structure, but it can provide useful information on purity and aggregation because modern SEMs can detect nanoparticles as small as 10 nm.

Transmission Electron Microscopy

This technology is a versatile, widely used, and effective nanomaterial characterization tool that can be used to determine sample size, ingredients, and its range. This technology is a commonly used and important technique for characterising nanomaterials, and it is used to measure distributional particles and/or grain sizes, as well as scale. TEM has advantages: which convey and allows for more in-depth analysis. One drawback is that a thin sample section is needed when using a high vacuum, and TEM's key characteristic is that it needs time to prepare samples. It is therefore remarkable to prepare a sample in TEM for the highest pictures available.

Properties of Silver Nanoparticles

Physiochemical properties of AgNPs, are all important factors in determining cytotoxicity. Shape is just as critical when assessing toxicity. Different forms of nanostructures have been used in the biomedical field, such as nano cubes, nanoplates, nanorods, nanoparticles, and floral-like nanostructures. The amount of biological and/or chemical coverage on the surface of AgNPs determines their toxicity. The surface charges of AgNPs could find out the toxicity effect in cells. For instance, because of the positive surface burden of NPs, they can stay in the bloodstream for long times compared with negative NPs. This is an important anti-cancer treatment tool.

Silver Nanoparticles used as a biomedical application

1. Silver compounds have been used in traditionally for ailments and cure since the beginning of human history.
2. Many easy, affordable, shield, and efficient methods, to make silver nanoparticles, wet chemical, physical, and biological methods can be used.
3. They can be made in a variety of shapes (poles, rods, circles, loops, squares) and sizes (from 2-100 nm) using prototypes and different reaction conditions.

4. Because of the close association between the silver surface and the thiol- or amine groups found in molecules such as organic molecules, DNA, proteins, enzymes, and so on, these are highly reactive due to a negative charge on the surface, allowing for the surface of AgNPs to be changed with a variety of biological molecules, which aids in various drug delivery processes.
5. AgNPs have strong antibacterial efficacy against a variety of bacteria.
6. Bacterial tolerances to metallic silver are exceptionally rare and display numerous bactericidal mechanisms that function together.
7. The fabrics and dressings of cotton shall indeed be mixed together in them, without any negative effect on the clothing.
8. They have a significant anti-inflammatory effect and benefit from a reduction of cytokine release and the reduction of lymphocyte and mathematical infiltration in the promotion of healing of wounds.

CONCLUSION

The current review is based on the current advancement of nano techniques for the development of carrier system as silvernanoparticle for targeted drug delivery at the particular site. The anti-inflammatory, anti-oxidant, anti-apoptotic, and anti-carcinogenic properties of silver nanoparticles are attracting the researcher's attention. Silver nanoparticles are the gift of nano technology in the field of pharmaceutics and medical industries. It precisely tailored to carry biomolecules to target cells, allowing for lower therapeutic dosages and fewer adverse effects. This review discusses that AgNPs play the important role towound healing. The present work includes the study of silver nanoparticles with various strategies. In this work, literature survey enhances the knowledge of latest technology for the feasibility of society.

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CHAPTER VII

PROLIPOSOMES: PREPARATION BY ROTARY EVAPORATOR

ABSTRACT

Liposomes are microscopic vesicles made up of a phospholipid bilayer and a unique drug delivery mechanism that delivers drugs at a predetermined pace based on need, pharmacological features, drug profile, physiological state of the body, and other factors. Liposomes have a poor stability problem, which makes them difficult to store. Pro-liposomes (PLs) were found in 1986 to solve this problem. Pro-liposomes are free-flowing granular products that turn into liposomes when hydrated. This research examines several aspects of pro-liposomes, including their preparation process, evaluation, and applications, as well as their potential for use in various administration routes.

Keywords: Liposome; Pro-liposome; Carriers; Phospholipids; Cholesterol

INTRODUCTION

Dr. Alec D Bangham, a British hematologist, originally described liposomes in 1961 at Cambridge. The liposome is made up of two Greek words: "Lipos" (fat) and "Soma" (body) and is effective, investigated, and widely used in all the new drug delivery technologies. A liposome is a tiny spherical vesicle with an aqueous center surrounded by phospholipid molecules. Drug compounds can be introduced into either the aqueous or lipid bilayer phases. They're commonly employed as a medium for delivering nutrients and pharmaceutical medications to improve the drug's stability and effectiveness by lowering negative effects. Liposomes must be stable and undamaged during storage to provide therapeutic action to be approved for the market. Liposomes are generally unstable colloidal structures due to physical and chemical instability to tackle liposomes, a new "pro-liposome" approach has been devised that can create liposomes quickly when needed and without significant modification. In 1986, pro-liposomes (PLs) were identified as seen in Figure 7-1.

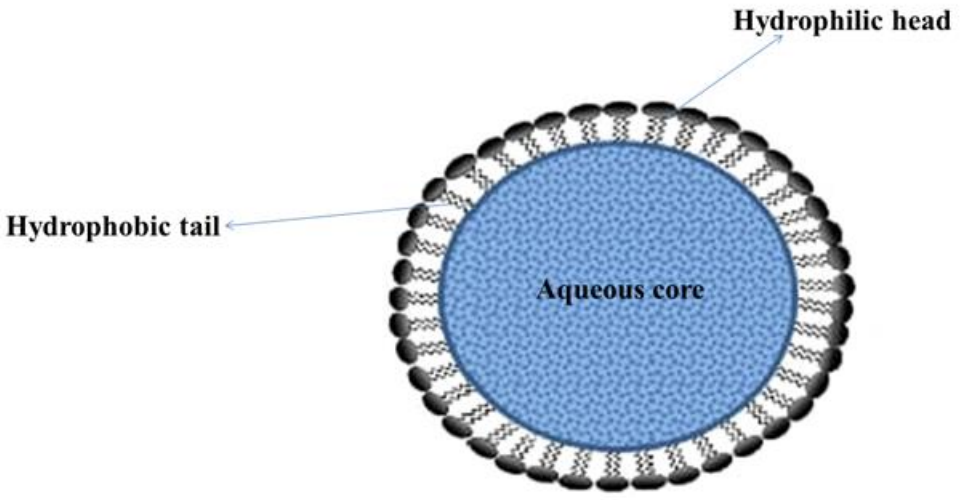

Figure 7-1: Proliposome structure with hydrophobic tail and hydrophilic head.

Pro-liposome materials that form liposomal dispersion when getting hydrated as shown in **Figure 7-2**. PL is a porous powder that is water-soluble and phospholipid. Payne et al. identified proliposomes [PL] in 1986, which are granules that are dry and free-flowing solids that form liposomal dispersion when wet. They're made comprised of phospholipids and a

water-soluble porous powder. Pro-liposomes are a widely used and cost-effective method for producing commercial liposomes. To make liposomal dispersions, proliposomes were mass-produced in enormous quantities. Membrane lipids that have been hydrated can generate vesicles on their own when they come into contact with water. The use of PLs as carriers for site-specific drug delivery systems is common. Many medications can benefit from proliposomal formulations, which increase drug bioavailability and help with solubility issues. At the administration site, maximum drug encapsulation enhances medication penetration and creates a long-lasting releasing action. Proliposomes have been proven to improve the solubility of a substance and bioavailability of some poorly soluble drugs, and they have been employed as the foundation site-specific drug delivery strategies as mentioned in Table **7-1**. Because they are available in dry powder form, they are simple to distribute, transport, measure, and store. Liposomes can be made in vivo with the use of physiological fluids or in vitro with the help of an appropriate hydration fluid before being injected. Liposomes formed during reconstitution are identical to regular liposomes; however, they are smaller and more homogenous in size.

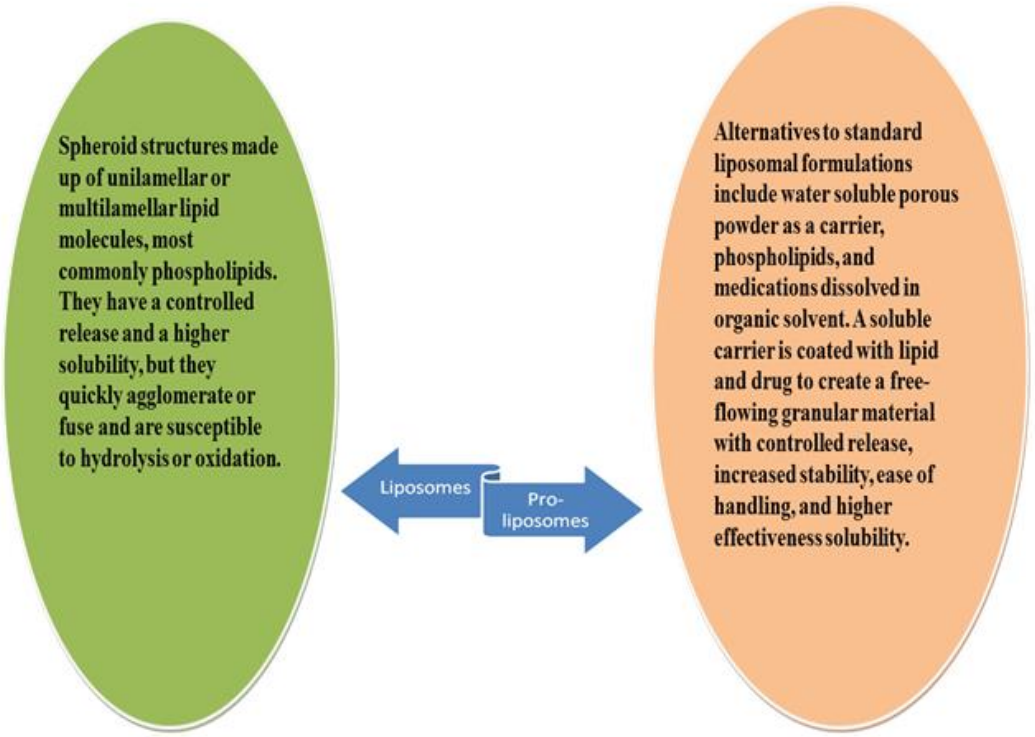

Figure 7-2: Comparisons between liposomes and proliposomes

Table 7-1: Approved Proliposomes as a drug carrier

S. No.	Route	Drug	Application
1	Oral	Domperidone	Priliposomes
2	Oral	Nimodipine	Proliposomes based soft capsule
3	Oral	Silymarin	Proliposome
4	Transdermal	Nicotine	Proliposomal gel
5	Transdermal	Metformin hydrochloride	Proliposomal gel
6	Transdermal	Repaglinide	Proliposomal gel
7	Nasal	Nicotine	Proliposome

8	Nasal	Propanolol HCL	Proliposome
9	Pulmonary	Levofloxacin	Proliposomes in a dry powder aerosol
10	Transdermal	Prednisolone	Proliposomal gel

ADVANTAGES

1. Proliposomes have a higher bioavailability.
2. The gastrointestinal tract protects drugs from decomposition.
3. Anti-cancer medications that is unique to the tumor's location.
4. By altering the phospholipid content of bilayers, proliposomes can be employed to regulate release within the vasculature.
5. Masking the taste and lowering the toxicity.
6. Proliposomes are a type of liposome that is utilized to deliver targeted therapy and regulate medication release.
7. It is reasonably priced.
8. It's quite easy to make.

COMPARISON BETWEEN LIPOSOMES AND PROLIPOSOMES

As mentioned in Figure **7-3**, Lipid spheroids are divided into two types: liposomes and proliposomes. Liposomes are spherical formations made up of unilamellar or multilamellar lipid molecules, most often phospholipids. When liposomes are exposed to hydrolysis, their solubility rises, and they clump or fuse. Liposomes are made up of a porous water-soluble carrier, phospholipids, and medications that have been soaked in an organic solvent. Liposomes are being phased out in favor of polymerized liposomes (PLs) when drug and phospholipids components are coated on carrier material, a free-flowing granular product with improved stability, solubility, and controlled release results.

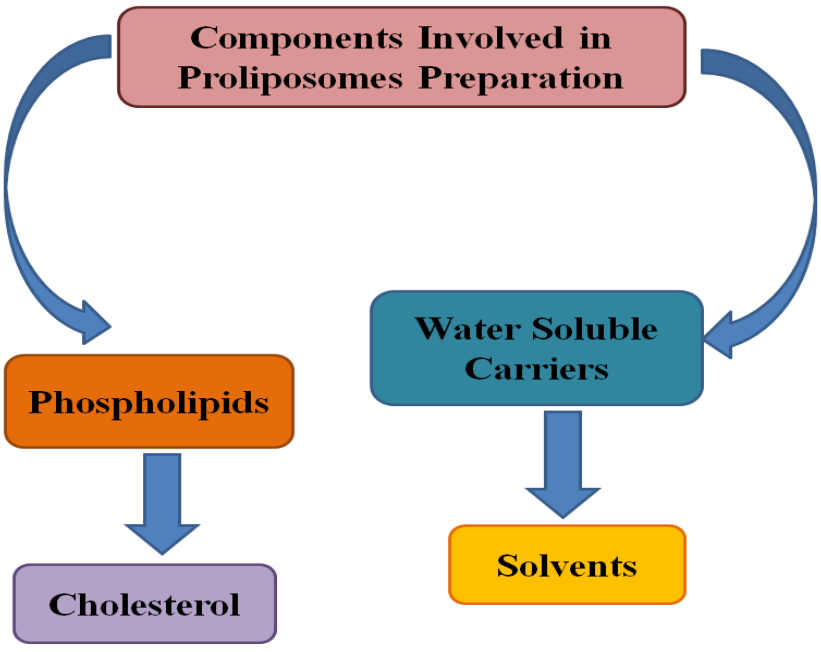

Figure 7-3: Component involved in proliposomes preparation

Components Involved in Proliposome Preparation

The physical and chemical features of phospholipids, which are vital in the structure and function of biologic membranes, have been the topic of evolving information regarding their physiologic relevance. Phospholipids have been proven to be dynamic structural components of membranes, contrary to popular belief. Within the membrane, phospholipids are in a dynamic state and may undergo physicochemical changes. This chapter main goal is to connect phospholipid pleomorphism to the physiological features of membrane and plasma lipoproteins. The production and catabolism of phospholipids, which McMurray and Magee address, have not been considered. The two forms of phospholipids that exit cellular membranes are phosphodiglycerides and sphingolipids. The most common phospholipid molecule is phosphatidylcholine (PC). Because phosphatidylcholine molecules are not water-soluble, they form planar bilayer sheets in aqueous conditions to prevent an unfavorable interaction between the bulk aqueous phase and the long hydrocarbon fatty chain. Glycerol-containing phospholipids account for more than half of the lipid weight in biological membranes, making them the most common component of liposome composition. These are made with phosphatidic acid. Phospholipids include Phosphatidylcholine (Lecithin) – PC, Phosphatidyl ethanolamine (cephalin) – PE, Phosphatidyl serine (PS), Phosphatidyl inositol (PI), and Phosphatidyl Glycerol (PG) (PG). Cholesterol plays an important part in the construction of Proliposomes, although the exact amount required to obtain an acceptable formulation is unknown. The major goal of this chapter is to study the most appropriate amount of cholesterol in lipids to construct stable and controlled drug release vehicles using a screening arrangement of lipids and cholesterol ratio. Phospholipids were mixed with different molar ratios of cholesterol (e.g., 80–20, 70–30, 60–40, and 50–50 percent) to make proliposomes. The formulations were tested for stability by keeping them at 37 and 50 °C for 30 days and analyzing them using AFM, DLS, and FT-IR. Cholesterol and its derivatives are frequently found as part of the liposomal membrane. It has three well-known effects when it is found in liposomal membranes. Increasing the membrane's fluidity or microviscosity, lowering its permeability to water-soluble molecules, and stabilizing it in the presence of biological fluids like plasma. Volatile organic solvents or solvent mixtures including ether, chloroform, methanol, and ethanol, are in charge of maintaining the suppleness of the vesicle membrane.

Methods of Preparation

To be regarded as acceptable, a "conventional" pharmaceutical product must meet specific chemical, physical, and microbiological stability requirements. These criteria can also be used to evaluate novel medication delivery techniques such as liposomes. Indeed, these criteria should be strict enough to rule out the possibility that slight changes in particle size, for example, could have a major impact on biodistribution and, as a result, efficacy. Proliposomes are an elegant alternative to standard liposomal formulations, which have a tendency to clump or fuse and are susceptible to hydrolysis. Lipids and drugs are coated on a soluble carrier to generate a free-flowing granular material that becomes an isotonic liposomal solution when moistened. This approach appears to overcome a lot of the problems associated with aqueous liposome dispersions. Furthermore, the proliposome technology allows for large-scale manufacturing at a low cost. The proliposome concept, in principle, should allow for a wide range of liposome formulations to be used. Certain phospholipid: carrier combinations, on the other hand, are not used in practice due to certain constraints. In this chapter, we'll go over the mechanism of proliposome hydration, as well as the effects of proliposome particle size and hydration temperature on liposome size.

Film-deposition on carrier method

The film deposition on carrier method is used to create Pro-liposomes. An evaporative solution containing a drug and phospholipids solution is injected drop by drop by a feed tube onto a core of carrier substance contained in a rotary flash evaporator vessel under vacuum, and the

medication and phospholipids coat is discharged on a pervious; water-soluble carrier substance in this method. Overwetting of the matrix is prevented at all times, and the next aliquot of the organic mixture is introduced only when the powder matrix is free-flowing. Select carriers should have a big surface area and permeability to control the amount of carrier required to aid the lipids. Furthermore, a high surfactant to carrier mass proportion is attainable in the manufacture of pro-liposomes. Because they are water-soluble, they allow for quick liposomal dispersion after hydration, and a very restricted range of reconstituted liposomes can be generated by carefully adjusting the size of the previous powder. Carriers such as maltodextrin, sorbitol, microcrystalline cellulose, magnesium aluminum silicates, mannitol, and others are frequently used. To eliminate the problem of sluggish solvent inclusion and evaporation, the carrier material is dispersed in an organic combination of medicine and phospholipids in a rotary evaporator vessel and then directed to vacuum evaporation. In comparison to the actual procedure, this results in a very consistent and well-organized lipid distribution, as well as a stable and less volatile lipid concentration.

CHARACTERISTICS OF PROLIPOSOMES

SEM

It's utilized to examine the PL powder's surface structure. It includes a comparison of a liposome image and a pure carrier material image. The presence of carrier material in the formulation indicates the presence of phospholipids on the carrier, and thus the formulation of proliposomes confirms this.

Hydration study

The hydration study is based on the notion that liposomes form when they come into contact with water. In this procedure, a little amount of dry pro-liposome powder is placed on a glass slide, which is then gradually filled with water, and vesicle formation is observed using a microscope. As soon as hydration is achieved, dissolution and disintegration begin. When water comes into contact with the lipid surface of proliposomes, liposomes form. This procedure is repeated until the lipid layer has completely hydrated and the carrier has disintegrated.

Transmission electron microscopy (TEM)

This procedure is also used to examine the structure of liposomes after they have been hydrated with PL powder. Using distilled water to hydrate the proliposome powder, examine the lamellarity and forms under a microscope.

Zeta potential

The zeta potential can be used to calculate a particle's surface charge. It's the potential difference between the solution's electro-neutral zone and the tightly bonded layer's surface (shear place). To make liposomes, a specified amount of proliposomes was diluted with distilled water. Using a Zetasizer 3000, the particle size of the liposomal suspension was determined.

Flow property

The flow feature of a powder formulation can explain content homogeneity and handling processing operation. It is required to examine the properties of the pro-liposome in a formulation based on solid powder. The following parameters can be measured to assess it: Angle of repose, Carr's Index, and Hausner's ratio are all terms that can be used to describe a situation**.**

Morphological characterization

Transmission electron microscopy (TEM) (JEM-2100, JEOL, Japan) was used to study the morphology of proliposomes (JEM-2100, JEOL, and Japan). The substance was diluted with distilled water and vigorously shaken to generate liposomal dispersion. microliter drop of solution was deposited onto a carbon-coated copper grid, which was then dried under bright

light until a thin liquid layer formed on one side. After being affixed to the end of a long iron rod, this dyed copper sheet was inserted into the TEM for sample viewing and photography.

Entrapment efficiency calculated

To hydrate a specific number of proliposomes, 100 mL of distilled water was employed (0.2 g). The liposomal suspension (1 mL) was combined with anhydrous alcohol (9 mL) and analyzed with a UV spectrophotometer (UV-2401, Shimazu, Japan) set to the maximum absorption wavelength of 255 nm. A blank liposome with a maximum absorbance of 208 nm did not affect the drug detection. The concentration of proliposomes can be mathematically calculated using the standard curve.

In vitro release studies

The in vitro release investigations were carried out using modest modifications to the release test method specified in China Pharmacopoeia (2010 edition, paddle method). After being exposed to distilled water, proliposomes containing 0.1 g prolioposomes were instilled into a dialysis bag (MWCO 3500 D, 25 mm5 m, Shanghai Green Bird Science and Technology Development, China). Before immersion in the dissolving media (pH 1.2 HCl, 900 mL; pH 6.8 phosphate-buffered saline, 900 mL) containing 0.1 percent sodium dodecyl sulfate as a surfactant, the dialysis bags were fixed to the paddles (sink condition). The entire set was placed on a dissolution tester (ZRS-8G, Tianjin University Radio Power Station, China) that was set to a constant speed of 100 revolutions per minute at 37 degrees Celsius. 10 mL was used at various time intervals.

Application of Proliposomes

PLs can be exploited for the following routes of administration

1. Parenteral Delivery

Sterilization is required before liposomes can be generated for parenteral use. Steam sterilization, -irradiation, aseptic production, and filtration sterilization are all commonly used sterilization processes in the pharmaceutical sector. Terminal sterilization with steam at 121^0C may not be appropriate for liposomal formulations, as high temperatures can damage liposome architecture due to lipid hydrolysis, resulting in physical destabilization. Irradiation is likewise ineffective for liposomal dispersions because it promotes hydrolysis and accelerates unsaturated lipid peroxidation. Because of the cost and difficulty of validation, aseptic production is not widely employed. Due to the structural complexity of these vesicles and the loss of lipids caused by their non-specific adsorption to filters, filter sterilization of the final product can be difficult. Liposomes are highly suited for parenteral administration via PLs [19]. The fundamental benefit of PLs is that they may be sterilized without changing their intrinsic characteristics. Furthermore, they can be sterilized and maintained in a dry condition before being hydrated and administered to produce multilamellar liposomal suspension. Furthermore, some recent investigations have found that sterilization by irradiation is not as harmful to liposomes as previously thought, especially when irradiated in the dry form. Hydroxyl radicals (produced when water is exposed to radiation) are a key source of free radicals that cause harm.

2. Dry Powder Inhalers (Dpis)

Inhaling the medication as a fine powder causes the substance to spread straight into the patient's airstream. Dry powder inhalers have several benefits, including regulated delivery, lower toxicity and potency, even local drug displacement, enhanced patient compliance, improved stability, and a significant amount of drug entrapment. Because pro-liposome formulations are in the form of dry powder, they are best used in a dry powder inhaler to administer liposomes. To prevent Pneumocystis carinii pneumonia, Dapsone dry powder inhaler with spray-dried liposomes entrapped has a prolonged therapeutic activity in the lungs. In vitro investigations show that the medicine takes 16 hours to release.

3. Nebulizers

It is the most straightforward way of delivering liposomes to the lungs, although it is susceptible to liposome leakage and drug instability. To solve this difficulty, dry powder formulations are used. As a result, pro-liposomes are effective carriers of liposomes via nebulization.

4. Pulmonary Delivery

Liposomal formulations for localized medication activity in the respiratory tract are also available. Because liposomes are made up of phospholipids, which are also found in lung surfactants, drug trapping inside them improves absorption. Drugs encapsulated in Liposomes stay in the bloodstream for longer periods and have fewer side effects.

5. Pressurized Metered-Dose Inhalers (Pmdi)

Liquefied propellants are mixed with a drug solution or suspension. Because they are non-ozone-depleting propellants, hydro Fluro alkanes are utilized instead of chlorofluorocarbons, however, they are weakly soluble in phospholipids. Proliposomes can be suspended in these propellants and used to transport liposomes into the lungs.

6. Oral Delivery

Pro-liposomes aid in the dissolving of medications that are difficult to dissolve. When it comes into contact with fluid, it generates multi-lamellar vesicles, which ensures greater trapping of insoluble medicines and allows the medication to be converted from crystalline to amorphous form. The greater particle size of multi-lamellar liposomes generated on hydration improves the bioavailability of medicines with extensive first-pass metabolism and increases lymphatic absorption. Liposome stability is improved with the use of pro-liposomes. Some poorly soluble medications benefit from formulations that increase their solubility and bioavailability. Works by blocking the 5HT3 receptor and Domperidone is poorly soluble in water and undergoes significant stomach and hepatic first-pass metabolism following oral treatment.

7. Proliposome In Ophthalmic Delivery

Proliposome in Ophthalmic, eye's unique defensive systems, achieving optimal medication concentration is difficult with ocular drug delivery. The development that achieves therapeutic concentration at the target site necessitates a thorough understanding of the eye's static and dynamic barriers. Because of their advantages as a carrier system, liposomes have been studied for ocular medication administration. They are nanocarriers and biodegradable. By adhering to the ocular surface and enhancing residence periods, they can improve the penetration of poorly absorbed drug molecules. Karn et al. produced a dry proliposome autoimmune illnesses, parasite infections, and inflammatory ocular surface disorders.

8. Proliposome In Nasal Delivery

Proliposome in Nasal delivery get attention in recent years as a convenient and reliable method for drug administration, not only locally but also systemically. Nasal medication delivery with proliposomes has also been demonstrated. Jung et al. performed to obtain longer administration providing a combination advantage of fast onset (surface drug) and prolonged drug action (encapsulated drug). Free-flowing proliposomes carrying propranolol hydrochloride were used in another fascinating**.**

9. Proliposome In Mucosal Delivery

Proliposome in Mucosal delivery is triggered by the aqueous environment found on the mucosal surfaces. Further, developed clotrimazole (CT)-containing vaginal proliposomes for prolonged drug release which resulted in increased antifungal efficacy. The aqueous environment prevalent on mucosal surfaces causes proliposomes to develop. They contain phospholipids, in the bilayers as molecular dispersion improves pharmacological action. The proliposomes change clotrimazole (CT)-containing vaginal proliposomes were produced by Ning et al. for delayed drug release, which enhanced the quantity of mucosa, resulting in increased antifungal efficacy.

CONCLUSION

Proliposomes are a new type of vesicular carrier that can solve the instability problem that plagues vesicular drug delivery. To create a proof-of-concept medication delivery system for a difficult drug that can be scaled up and released in a regulated manner. Proliposomes are chemically and physically stable, and they may be scaled up commercially. Because of their low toxicity and great lipid penetration, proliposomes are also a viable option for transdermal medication delivery. Proliposomes play an important role in the distribution of oral drugs in the form of tablets, capsules, and dry powder for a variety of administration routes. The pulmonary distribution of proliposomes as dry powder allows for direct targeting of lung tissues while avoiding the drawbacks of the oral route and providing a non-invasive alternative to the parenteral route.

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CHAPTER VIII

CARBON NANOTUBES: SMART DRUG DELIVERY

ABSTRACT

Carbon nanotubes are one of the few materials that have received such high praise Carbon nanotubes (CNTs) are coiled graphene sheets held together by van der Waals forces that were discovered in Japan in 1991 by Sumio Iijima. Because of their strong connections, carbon nanotubes cluster together and create massive aggregates.CNTs have amassed an impressive list of superlatives since their discovery in 1991, and are often regarded as the archetypal nanomaterial. Carbon nanotubes are the ultimate carbon fiber, with the strongest and the highest thermal conductivity, as well as remarkable field emission properties. Metallic carbon nanotubes do not dissipate heat and conduct electric current in a ballistic manner. Because of their unique topologically controlled electrical characteristics, they can also operate as an active semiconductors in nanoscale devices. Carbon nanotubes were first studied by scientists who were intrigued by their distinctive physical features, but in recent years, interest has shifted to their chemical properties. As a result, this special issue of Accounts of Chemical Research, which features articles from some of the world's leading experts on carbon nanotubes, is both timely and useful for the chemical community. Carbon nanotubes' ends and walls are functionalized.

INTRODUCTION OF CARBON NANOTUBES

The discovery of nanometer-sized carbon tubules, followed by the discovery of conditions enabling the synthesis of massive amounts of nanotubes, triggered a surge in interest in carbon nanotube research. Since these early reports, much research has been conducted, and the results show that carbon nanotubes behave similarly to rolled-up cylinders of graphene sheets with sp2 bonded carbon atoms, with the exception that the tubule diameters in some cases are small enough to exhibit one-dimensional (1D) periodicity effects. When a team from the Naval Research Laboratory originally submitted a theoretical article on the electrical structure of such small tubes in 1991, the findings were deemed too speculative for publication since nanotube production appeared impossible shortly. The researchers hypothesized that, unlike graphite, merely converting a sheet of graphite into a tiny tube would result in a structure with a carrier density close to that of metals. They also projected that, unlike other conjugated materials like polyacetylene, the tube will have no Peierls distortion (bond alternation leading to the creation of a gap) at room temperature. Simultaneously, Sumio Iijima of NEC was analysing a sample of carbon soot obtained from Yoshinori Ando of Meijo University using transmission electron microscopy. The sample was taken from a carbon arc machine that is often used to generate C60. Tubules were found in the sample, according to Iijima. The enthusiasm around this finding was heightened when various theoretical analyses suggested that, depending on the diameter and helicity, the nanotube might be either metallic or semiconductor. Carbon nanotubes were viewed as the ultimate fiber from a materials standpoint, with an excellent strength-to-weight ratio. As a result, by the spring of 1992, nanotube expectations were sky-high. The problem was that the nanotubes were only found in trace amounts in the carbonaceous deposits, making it difficult to extract them or study their properties. Great strides have been achieved in the field of nanotechnology in recent years, notably in the production of sensors with a wide variety of applications. Nanomaterials, which are measured on a nanoscale, are the cornerstone of nanotechnology Dr. Richard P. Feynman, a well-known physics professor, proposed the first concept in 1959. Norio Taniguchi, a Japanese scientist, coined the term "nanotechnology" in 1974. "Nanotechnology," he explained, is the partitioning, joining, and twisting of materials by molecules or atoms. A nanometer is one billionth of a metre, which is substantially smaller than the visible light wavelength. Nanotechnology has an impact on both technology and health, a

wealth of human beings that investigate the fact of structures and materials. We were well recognized for various kinds of carbon, including diamond, graphite, and amorphous carbon, until 1980. Following that, we now know all carbon forms. A new form was introduced in 1985. It is in the shape of a 1D, which causes many appealing features to change or be added, such as mechanical, electrical, and molecularIts structure is similar to that of a cylindrical molecule with a hexagonal arrangement of sp2-hybridized carbon atoms. It features a hollow interior and a surface composed of single or many layers of graphene sheets. NEC and IBM announced in 1993 that CNT is made up of a single graphene sheet. Iijima leads a group of newly-found research. CNT has a unique property that has made it a powerful parameter in both research theory and application. Carbon nanotubes are currently the most important group. Carbon nanotubes are composed of one or more concentric graphite-like layers with diameters ranging from 0.4 to tens of nanometers. Iijima discovered the field of carbon nanotubes in 1991, following an early TEM (Transmission electron microscopy) discovery of carbon nanotubes and later reports of circumstances for the synthesis of significant volumes of nanotubes. Carbon nanotubes (CNTs) are carbon-based tube-like compounds with nanometer-sized diameters. They're formed of graphite sheets, and the graphite layers resemble a non-stop, unbreakable hexagonal mesh structure, with carbon molecules appearing at the apexes of the hexagonal formations. Depending on the number of carbon layers, carbon nanotubes are classed as single-walled carbon nanotubes (SWCNTs), double-walled carbon nanotubes (SWCNTs), or multi-walled carbon nanotubes (MWCNTs). The three basic methods for manufacturing carbon nanotubes are chemical vapor deposition, electric arc deposition, and laser deposition (CNTs). High elasticity, high thermal conductivity, low density, and chemical inertness are only a few of the qualities that differentiate carbon nanotubes. They are used in nanotechnology, electronics, optics, and other fields as shown in Figures 8-1.

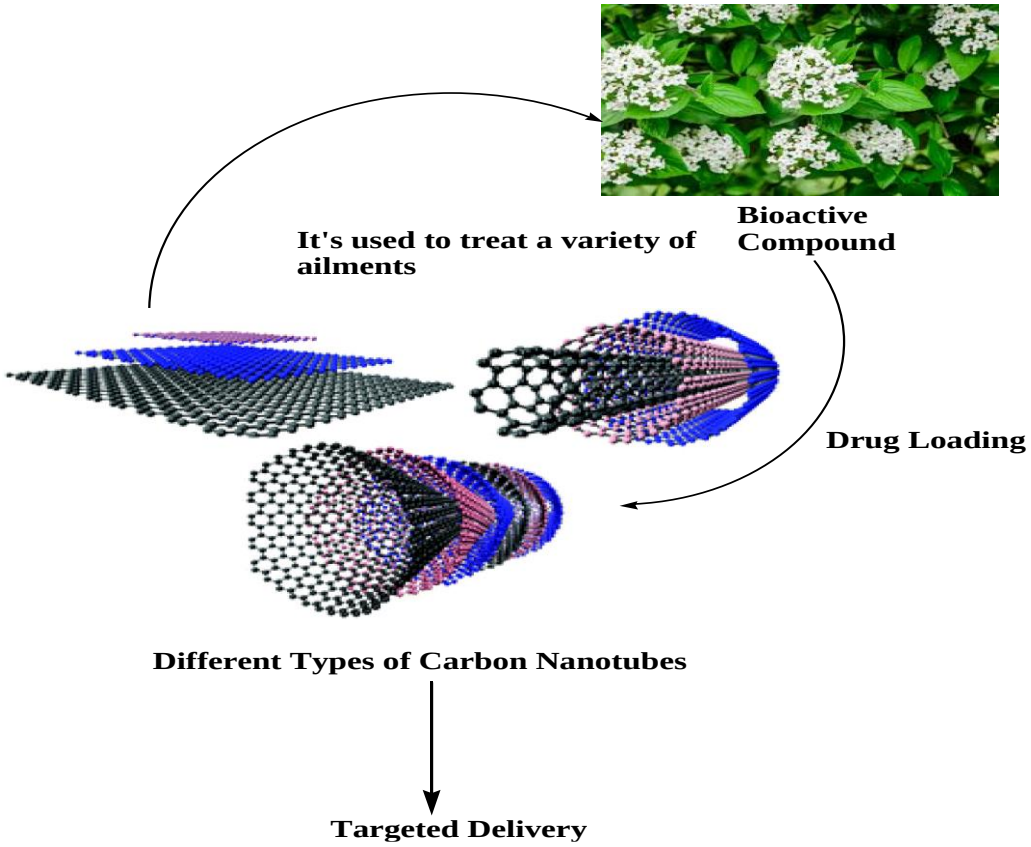

Figure 8-1: Carbon nanotube uses in biomedicine are depicted schematically

DEFINITION

CNT is constructed up of a single graphene sheet, according to NEC and IBM in 1993. Carbon nanotubes consist graphite sheets that have been rolled into cylindrical shapes.

Carbon nanotubes (CNTs) are a hybrid of carbon fibers and fullerene, containing 60 carbon atoms arranged in small tubes. Carbon nanotubes are divided into two groups. SWCNTs are hexagonally packed bundles made up of a single graphene layer with a diameter ranging from 0.4 to 2 nm. MWCNTs (multi-walled carbon nanotubes) consist of two or more graphene cylinders. The diameter varies from one to ten centimeters. Sumiolijima discovered CNTs in 1991, and his first effort was to make a multi-walled carbon nanotube using a basic arc evaporation approach. CNTs consist of carbon atoms with a diameter of 3–15 nm and are organized in hexagon and Pentagon shapes, Kroto et al. discovered CNT, a subtype of fullerene that is made up of carbon allotropes, in 1985. Nanotubes get their name from their size, as a nanotube's diameter is only a few nanometers. These are massive macromolecules that are one-of-a-kind in terms of size, form, and characteristics. CNTs are spherical constructions enclosed by moving single perhaps several layers of graphene sheets. Count on the amount of essence in the outer layer or wall. As illustrated in Figure 8-2, When we have started to discuss the structure of nanotube we must become through fullerene because nanotube constitutes fullerene. When a sheet of Fullerene is rolled at specific and separate angles then a proper structure of nanotube will be formed with a fixed inner radius. Due to the role of a graphene sheet, by itself it forms various allotropes of carbon; also incorporate with graphite and fullerenes its form CNTs.

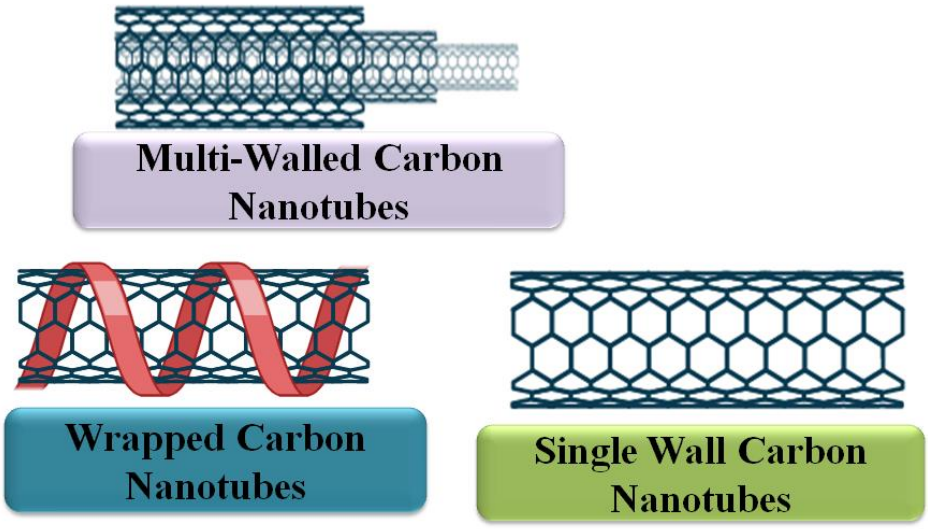

Figure 8-2: A carbon nanotube is seen in this diagram

TYPES OF CARBON NANOTUBES

Single-walled CNTs In 1993, the term "single-walled carbon nanotubes" (SWNTs) was coined. A single layer of graphene sheet with a diameter of 1–2 nm is used to make SWNTs. For proper control over improvement and atmospheric state, a catalyst is essential for the synthesis of CNTs. CNT length may vary according on the preparation procedure, resulting in poorer purity. CNTs with two walls Double-walled carbon nanotubes (DWNTs) are composed of two carbon nanotubes connected by an outer tube that encloses the inner tube. The outer tube has a diameter of 2–4 nm, whereas the inner tube has a diameter of 1–3 nm. CNTs with many walls Because many layers of graphene sheet folded with widths varying from 2 to 50 nm are present. The presence of graphene sheets gives MWNTs their names and numbers. The inner layer radius of the tube is 0.34 nm, whereas the outer layer radius spans from 2 nm to 20–30 nm.

Synthesis of CNTs

Electric arc discharge method Iijima disclosed the tube's manufacture in 1991, using the arc discharge evaporation method, which is similar to the prior fullerene synthesis method. Carbon needles with diameters of 4 to 30 mm and lengths of up to 1 mm were formed on the negative end (cathode) of the carbon base electrode for CNT production. Iijima's high-resolution electron micrographs of CNT at 500tr under helium are displayed in the chamber, which contains graphite as a cathode, evaporated carbon molecules as an anode, and metal catalysts such as cobalt, nickel, and iron. The chamber is compressed and heated to 4000 degrees Fahrenheit (approximately). The power supply and the two graphite rods are separated by a few millimeters. The carbon begins to evaporate after turning on the source and maintaining a current of 100 amps

The catalyst precursors would be useless if they weren't available. Laser ablation method These et al., in 1996, used the laser ablation approach to lower CNT production by 70% by using a limited quantity of Ni and Co at 1200°C. The laser's ultimate purpose is to melt the graphite within the quartz. As the power of the laser pulse increased, the diameter of the tubes shrank. Laser ablation maintains constant pressure due to the use of helium or argon. The structural and chemical makeup of the target materials is two properties that are impacted by laser ablation technologies. Thermal synthesis process Plasma-based synthesis includes. Thermal energy is managed and the temperature never exceeds 1200°C. In the case of plasma-enhanced CVD, a similar technique will be used. Fe, Ni, and Co is active catalyst materials. CNTs are reliant on carbon as a feedstock in this application.

The thermal approach of CNT synthesis is the most convenient for various chemical vapor deposition processes. These techniques include chemical vapour deposition, monoxide synthesis, and flame synthesis. There will be a case of plasma-enhanced CVD included. Active catalyst materials include Fe, Ni, and Co. In this application, carbon nanotubes rely on carbon as a feedstock. The approach is capable of controlling the development component as well as generating a huge number of nanotubes. A reaction can change the presence of volatile substances into the required solid layers. At room temperature, fullerene is synthesised using CVD. The horizontal and vertical fullerene configurations are employed here. Place the substrate in an oven and heat it to 700°C-900°C before progressively adding carbon-bearing gases such as acetylene, methane, or ethylene, as well as nitrogen, into the response chamber. Vapor-phase growth Vapor phase growth is a CVD process that has been advanced and modified. Ferrocene is used as a catalyst in this approach, and two low-temperature furnaces are located in the response chamber. Throughout the process, fine catalytic particles are created in the first furnace, and when they reach the second furnace, carbons are propelled into the catalyst through diffusion and transformed into CNTs. Method of generating flames Another possibility is to employ a flame as a source of CNTs. The flame is employed as a synthesis medium, delivering both energy and chemical species at the nanoscale in the form of different forms of carbon. Fuel (gases such as methane (CH_4), ethylene (C_2H_4), and acetylene (C_2H_2), among others) is combined with an oxidizer to produce a different gaseous mixture containing carbon dioxide (CO_2), water vapor (H_2O), carbon monoxide (CO), hydrogen (H_2) saturated and unsaturated hydrocarbons (C_2H_2, C_2H_4, C_2H_6), and radicals. Catalytic activity is required to provide reaction sites for solid black carbon deposition. In compared to other approaches, the flame synthesis method is an auto-thermal process that can provide temperature to achieve the required synthesis state. The vaporised catalyst may be injected using a flame. Flames are scalable, and they're employed commercially to make solid carbon forms like carbon black and printing ink. Plasma-enhanced chemical vapor deposition The temperature may be decreased using this CNT manufacturing approach. When compared to CVD, the PECVD approach is more effective at keeping the temperature low and controlling the development mechanism. The plasmatic energy successfully dissociates gas molecules in PECVD, and CNTs begin to grow at

low temperatures. It has two orders of magnitude higher development rates. The most important component in the creation of SWNT is plasma. The plasma mode of a PECVD air pressure radio-frequency discharge (APRFD) reactor altered the input power from mode (60 W) to mode (60 W) (100 W). An benefit of using the PECVD technique is the built-in electric field that occurs in a plasma sheath when altering the growing CNTs. Drug smuggling Using multiwalled carbon nanotubes, drug targeting and controlled drug release are both conceivable. Targeted medication delivery occurs when a potent therapeutic medicine is supplied to a specific portion of the body over an extended period. Carbon nanotubes are employed in medication delivery because of their hydrophobic nature, which permits them to remain in the circulation system for a long time. Due to varied stimuli that can be regulated by carbon nanotubes, such as magnetic stimuli, electric stimuli, temperature change, used to target and controlled drug delivery. Carbon nanotubes are used to transport biomolecules, including proteins, DNA, RNA, immunoreactive chemicals, and lectins. The involvement of MWCNT and pH-responsive gel in the distribution of doxorubicin medication was detailed by Seyfoori et al., 2019. MWCNT and pH-responsive gel, i.e. chitosan-coated magnetic nanocomposites, produced the nanohybrid system. The nanohybrid system created was meant to deliver the drug to U-87 Glioblastoma cells, and it was revealed that when the medicine was delivered via the nanohybrid system, tumour proliferation was inhibited. Meherjuoi et al., 2017 compared different nanotubes for Cisplatin medication delivery. Because they used Ag Nanowires as a stimulator to release the medication from the interior of nanotubes, this technique of molecular dynamic phenomena was established. Their nanotubes, namely carbon nanotubes, silicon carbide nanotubes, and boron nitride nanotubes, were compared in this method. The findings showed that the composition and diameter of nanotubes affect medication release efficiency. The findings also revealed that drug release kinetics are quick and unrelated to nanotube structural composition. Servant et al. (2013) created an electroresponsive polymer-MWCNT hybrid hydrogel with pulsatile sucrose release. They evaluated the controlled releasing profile using radiolabeled sucrose as a hydrophilic drug model and an electric field. Mandal and colleagues (2016) investigated the long-term diclofenac sodium release of a multiwall carbon nanotube and a biodegradable, biocompatible nanocomposite hydrogel. The polymer composite of multiwall carbon nanotubes (MWCNTs) was shown to be a better alternative to the transdermal formulation because it delivers diclofenac sodium in a more consistent and long-lasting manner. Cell uptake of CNTs the ability of medicines and other extracellular species to overcome the cellular barrier is critical for the development of new biomedical therapies. As a result, many drug-delivery systems rely on a 'transporter,' which is a platform capable of being loaded with a cargo of choice and carrying that cargo through the cellular membrane without compromising its biological functioning. CNTs are versatile, innovative nano-carriers for medication delivery systems, and they are currently being investigated.

CNTs can permeate the cell membrane and be taken up by cells due exceptionally high aspect ratio. After entering the cell, CNTs are typically located inside endosomes and lysosomes. Individualized carbon nanotubes may cross cellular barriers and even reach the nucleus. The endocytosis-phagocytosis route and passive diffusion are the relevant cell-internalization pathways for CNTs. Briefly, Endocytosis is the process of a cell absorbing an external particle. cell (for example, viruses with a size of less than 100 nm) by the development of After then, the vesicle is integrated into the cell. Phagocytosis is a comparable condition. Endocytosis is similar to phagocytosis, except it usually involves the ingestion of bigger particles, such as bacteria. as bacteria (one meter) These two processes are both energy-intensive. At low temperatures, they are hampered.

Several investigations have been conducted in this sector to determine the precise absorption process of various types of CNTs. The predominant internalization process of SWCNTs bound to diverse types of proteins to be energy-dependent endocytosis.

MWCNTs that were shorter (i.e., b1 m) were readily absorbed by cells, whereas those that were longer were not. Short carbon nanotubes can operate as straight 'nano-needles,' piercing the cell membrane more easily than longer CNTs, which are commonly coiled or bundled, preventing efficient uptake.

Covalent Attachment

Due to van der Waals forces, pristine (as-prepared) CNTs readily congregate in bundles and so cannot be disseminated efficiently in physiological aquatic conditions. Chemical alteration of the CNT surface, also known as 'functionalization' or f-CNT, is one approach to exfoliating the bundles. Chemical grafting of molecules onto the sp2 carbon atoms of the -conjugated skeleton of CNTs is known as covalent functionalization. Oxidation under severe acidic conditions is the basic step for CNT functionalization. Carboxyl groups are produced first, then near flaws, shortening the CNTs in the process. Furthermore, the acid functions can react with alcohols or amines to form ester or amide connections. Although oxidized carbon nanotubes are soluble in water, they agglomerate and hence cannot be used directly in biological applications. As a result, additional modifications are required, such as adding hydrophilic polymers, such as polyethylene glycol (PEG), to generate CNT-polymer conjugates that are stable in physiological settings. Due to the oxidative process, this technique has the disadvantage of causing partial loss of electrical structure as well as material loss. Nonetheless, in drug-delivery applications, these concerns are less important. Covalent coupling can also be used to create a tumor-targeted medication delivery system.

In vitro studies revealed a quick reduction in tumor size when compared to non-targeted SWCNT, ensuring optimum medication efficacy with minimal side effects. Another common covalent modification is the 1,3-dipolar cycloaddition of azomethine produces, which is produced by condensation of an R-amino acid with an aldehyde; this reaction is commonly used to modify CNTs organically. After all, the preparation procedure only involves sonication and centrifugation. 'Click chemistry,' coined by K. Barry Sharpless, is a set of chemical reactions that meet several requirements, including modularity, wide scope, high yield, and stereospecificity. Several biocompatible compounds, as well as some proteins, used for pure CNT dispersion. The creation of 1,2,3-triazoles the most common reactions in this sector. The catalyst (in most cases, copper) gives preferential access to the triazole's 1,4-regioisomer and allows the reaction to take place at room temperature. This process is utilized to modify the surface of nanomaterials and biomolecules as well as functionalize them. At ambient temperatures and pressures, these extremely stretched alkynes react selectively with azides to generate regioisomeric mixes of triazoles, without the need for metal catalysis and with no apparent cytotoxicity. One of the biggest issues with employing carbon nanotubes as drug nanocarriers are that they are mistaken for foreign particles in the bloodstream. CNTs interact with opsonins, and blood serum components, mostly through hydrophobic and electrostatic interactions. These components are recognized by reticuloendothelial system (RES) macrophages, which remove CNTs from the bloodstream in seconds. CNTs treated with PEG can also be distributed in aqueous solutions with a greater salt concentration. The influence of a polymer surface coating on CNT behavior in vivo was investigated. PEG of various molecular weights (PEGylation degree) is initially linked to CNTs. Raman spectroscopy was used to investigate the blood circulation of CNT-PEG in animals with breast cancer tumors. CNT was found to have minimal RES buildup, high tumor absorption, and poor skin retention when conjugated with PEG.

Applications of CNTs Cancer diagnosis and treatment

Cancer diagnosis and treatment have both used multi-walled carbon nanotubes. Shows how MWCNTs are used in cancer treatment. Wang et al. discovered in 2014 that narrow multiwalled carbon nanotubes (09.2 nm average diameter) exhibited better tissue affinity, than larger

multiwalled carbon nanotubes (39.5 nm average diameter). In vitro breast cells, Samori et al. delivered the anticancer medication methotrexate using multiwalled carbon nanotubes and an enzymatic cleavage release mechanism. Similarly, the drug doxorubicin (DOX) was delivered at low pH using dendrimer-modified multiwalled carbon nanotubes. In 2015 Guo et al.; developed carrier cationic Multiwalled carbon nanotubes-NH3+ used to deliver the apoptotic siRNA against polo-like kinase (siPLK1) in tumor xenografts by direct intertumoral injections. In the near-infrared (NIR) bands (NIR I: 700-900 nm, NIR-II: 1–1.4 m), CNTs have a high optical absorption.

The penetration depth of NIR optical light into biological tissue is 1.6 mm. CNTs generate heat through light absorption and cause cancer cells with adequate CNT concentrations to be thermally destroyed. Targeted CNTs have been created by covalently attaching tumor-specific ligands to the CNTs to avoid harm to normal tissues.

Under physiological settings, the conjugated CNTs are stable and produce a highly selective photothermal death of the targeted cells. Internalized CNTs are more vulnerable to photothermal damage caused by NIR. Laser irradiation of mitochondria-targeted PEG-SWCNTs selectively kills malignant cells. Because of their increased mitochondrial transmembrane potential, dispersed PEG-SWCNTs readily aggregate in cancer cells' mitochondria and cause high levels of tumor cell death in mice with considerable apoptotic features. On solid malignant tumors, the effect of intra-tumor injection of PEG-SWCNT followed by NIR irradiation was studied in vivo. The malignancies were destroyed with no negative side effects. In addition, the majority of SWCNTs were eliminated from the body within two months. Other experiments using different types of CNTs, such as DNA-coated MWNTs and phospholipids-PEG-folic acid–SWCNT, backed up similar findings. The inherent fluorescence (NIR-II range) of the CNTs utilized to observe the course of the SWCNTs through the mice's anatomy. However, the similar things get reversed in a liquid medium. Short tube aggregates in a liquid medium contain a low number of cells than long tube aggregates. During the aggregation process, long tube aggregates might include a larger number of cells. Diameter also plays a role, since a smaller diameter leads to closer interaction with microorganisms, whereas a larger diameter leads to less interaction with microbes.

As a result, the aspect ratio of MWCNTs was crucial in determining their antibacterial properties. Multiwalled carbon nanotubes functionalized with mono-, di-, and tri-ethanolamine demonstrated greater antibacterial activity than pure Multiwalled carbon nanotubes, according to Zardini et al., 2014. Antimicrobial activity was proven against four-gram positive and four-gram negative bacteria.

Antifungal activity of CNTs

Rathore et al. (2000) used the agar well diffusion technique to demonstrate antifungal activity in vitro. In this technique, chitosan derivatives are combined with MWCNT to display antifungal action against fungi such as A. niger, C. tropical, and C. neoformans. The nano-composites have a lot of potential because the polymer chitosan inhibits spore germination, germ tube elongation, and radial growth. Chitosan stimulates cell wall morphogenesis, which inhibits fungus growth.

Gene Therapy

Gene therapy is a new type of molecular medicine that entails discovering DNA sequences and then devising effective methods for delivering this genetic material to cells. Immunogenic, oncogenic, inflammatory, and difficult to functionalize by ligand targeting viral vectors are all possibilities. Nonviral vectors, which use synthetic liposomes and polymers to host bare DNA, provide an alternative. However, the majority of these vectors are unable to pass the nuclear membrane. CNTs are being investigated as a solution to this and other problems non-viral delivery mechanism, due to their capacity to cross both the viral and non-viral due to their

favorable pharmacokinetics and nuclear membrane. Because biological enzymes degrade DNA, the DNA payload must be protected during long-distance transport. When compared to free DNA, SWCNT-modified DNA exhibits higher transport capabilities and intracellular biostability, indicating that it has considerable potential in this area. Ammonium-functionalized CNTs associated with plasmid DNA via electrostatic interactions.

CONCLUSION

Because of their unique features, carbon nanotubes (CNTs) have a lot of potential in the biomedical field. This review aims to draw attention to the most recent biomedical applications of CNTs while taking into account potential stumbling blocks such as toxicity concerns Biosensors, vaccine nano-carrier, soft tissue substitutes, and other tissue engineering applications are a few other bio-related applications not covered in depth in this chapter. We've shown how CNTs' versatility is demonstrated by their diverse structural (e.g., length, diameter), chemical (e.g.,attached functionalization), and physical properties, indicating that they can be used as nano-carriers for targeted drug delivery. Multiple drugs or targeting agents can be attached to CNTs in a variety of ways.

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CHAPTER IX

MICELLES FORMATION

ABSTRACT

Advances in block copolymer syntheses have led to polymeric micelles that may serve as nanoscopic drug carriers. Micelles were synthesized from biocompatible and biodegradable block copolymers for medication delivery. Polymeric micelles have functional groups on their surfaces that allow pilot molecules to bind. Researchers are developing chemical and physical methods for putting medicines into polymeric micelles. Particularly polymeric micelles solubilize hydrophobic medicines that are insoluble in water. Recent research indicates that polymeric micelles may contain solid-like centres. As a result, they may remain intact for extended periods of time under sink circumstances and may also slowly release pharmaceuticals. Polymeric micelles can operate as medication transporters by overcoming host defenses. Circulating over extended periods of time and extravagating from the circulatory system, delivering a medication to solid tumors preferentially. Micelles are dynamic aggregates formed in aquatic settings from molecules with both hydrophilic and hydrophobic properties. Micelles, as these aggregates are known, have piqued people's interest. The field of micelles in analytical chemistry has grown to the point where it is now difficult to contain all of the required areas of analytical technology within one review. Several of the subspecialties of analytical chemistry deserve and have received the utility of micelles within those disciplines. Armstrong has written an excellent point concerning the area of separations and micelles, while the field of micelles in electrochemical measurements by McIntire. The hydrophobic and hydrophilic characteristics of an amphiphilic molecule are clearly defined. A system of surfactant dispersed in an aqueous medium called "micelle" or "regular micelle" when no qualifiers are included. The non-polar component of the molecule is known as the (hydrophobic) tail in these conventional micelles, whereas the polar structure is known as the (hydrophilic) head group. Whenever the concentration of these molecules in solution surpasses a particular limit, known as the critical micelle concentration (CMC), they clump together to form micelles, which are well-defined aggregates.

Keywords: Hydrophilic, Hydrophobic, Critical Micelle Concentration, Amphiphilic

INTRODUCTION

Liposomes, polymeric micelles, nanogels, nanocapsules, dendrimers, carbon nanotubes, nanocrystals, and solid lipid nanoparticles are among the nanoscale systems being investigated for the delivery of small molecule drugs as well as therapeutic macromolecules such as proteins, peptides, aptamers, and DNA (Torchilin, 2006; Peer et al., 2007; Wang et al., 2012a). Many drawbacks of free pharmaceuticals can be overcome using nanomedicines, including limited solubility, non-selective action, poor biodistribution, toxicity, and multi-drug resistance (Allen and Cullis, 2004; Jabr-Milane et al., 2008; Sawant et al., 2012). Nanocarriers have several advantages, including increased drug stability, the ability to solubilize hydrophilic and hydrophobic agents, improved PK and biodistribution, tunable payload release, the ability to specifically target their payload to diseased tissues and cells by modifying their surface chemistries, and finally, the ability to respond to various internal and external stimuli for "triggered" release to achieve temporal and spatial control over the release of t (Torchilin, 2006; Peer et al., 2007; Duncan and Gaspar, 2011; Schroeder et al., 2012). However, because of the inherent benefits of nanomedicines over traditional therapies, the quick speed of nanocarrier development, and the scarcity of extensive systemic toxicological research on them, it is easy to ignore some toxicity problems. It is crucial to recognise that material characteristics at the nanoscale range change dramatically from those found in bulk, with greatly increased surface-

to-volume ratios, altered surface chemistry, and enhanced chemical reactivity (Elsaesser and Howard, 2012). Due evaluation of these elements could lead to the development of dependable nanosystems with a variety of promising characteristics.

Polymeric micelles

They are used due to their good biocompatibility, low toxicity, increased blood circulation time, and capacity to solubilize large amounts of pharmaceuticals in their micellar core. Polymeric micelles are divided into conventional, polyion complex micelles, and non-covalently linked polymeric micelles based on intermolecular forces.

Direct dissolving, solvent evaporation, and dialysis are the three options. Critical micellar concentration, size and shape, and in vitro drug release behavior were used as evaluation approaches. In aqueous media, drugs and therapeutic chemicals that are routinely employed to treat illnesses have a low solubility. As a result, a growing focus on the creation of drug delivery systems that are both highly competent and site-specific is seen. As more complex synthetic compounds enter the therapeutic sector, delivery systems must evolve to accommodate this feature. Such complicated compounds can be delivered using the micellar delivery technique. Polymeric micelles are a sort of colloidal particle carrier that self-assembles in the aqueous medium. They have a linear amphiphilic macromolecule with hydrophilic and hydrophobic blocks. Polymeric micelles have a particle size of 10 to 100 nanometers. Liposomes are much larger. The efficiency of the drug delivery system of block copolymer aggregates is influenced by two main factors: temporal and distribution controls. The time necessary for drug release from the micelle core is described by temporal control, as is the mechanism of drug release. Controlling the distribution and buildup of drugs known distribution control.

Micelles Definition

Micelles, according to IUPAC, are colloidal particles that exist with the molecules in equilibrium in the solutions. Micelles are useful in the pharmaceutical industry because they increase the solubility of water-insoluble substances. In an aqueous solution, a typical micelle has a hydrophilic head and a hydrophobic tail. The solvent molecules are phased by the hydrophilic head, and the hydrophobic tail forms a core. The aggregation number can range from 50 to 200nm. The self-association of amphiphilic molecules is triggered by a decrease in the free energy of the system. The size of the hydrophobic domain, and the amount of amphiphiles present, in the temperature, and the solvent all impact micellar development. Aggregates form when the concentration of amphiphilic molecules surpasses a particular threshold; this threshold is known as critical micellar concentration (CMC). Amphiphilic compounds exist separately at low concentrations. Monomers occur at the interface at CMC, causing the bulk phase to become saturated. The core consist of a hydrophobic tail that is utilized as load therapeutic active drugs. The shell reacts with the solvent, forming nanoparticles that are liquid stable. Polymeric micelles have a diameter of 10 to 100 nanometersThe molecular weight of amphiphilic block copolymers, the amphiphile's aggregation number, the properties of hydrophilic and hydrophobic chains, and the manufacturing technique all impact the size of polymeric micelles. A stimuli-sensitive copolymer is employed in the development of intelligent vehicles. In an aqueous environment, polymeric micelles are spherical, nano-constructs (10–100 nm) that contain both hydrophilic and hydrophobic units (Yokoyama et al., 1998; Jones and Leroux, 1999; Torchilin, 2001, 2007; Croy and Kwon, 2006). (Torchilin, 2001; Sutton et al., 2007). The hydrophobic component of the block copolymer produces the core of micelles, while the hydrophilic portion forms the shell (Figure 9-1). Micelles of amphiphilic copolymers with low CMC values are frequently more stable in the medium, even at low amphiphile concentrations. The CMC is lowered by enhancing the copolymer's hydrophobicity, which enhances micelle stability. (Torchilin, 2001; Kabanov et al., 2002). Non-polar molecules are dissolved within the micelle's hydrophobic core, polar molecules are adsorbed on the surface

of micelle, and molecules of intermediate polarity are distributed.

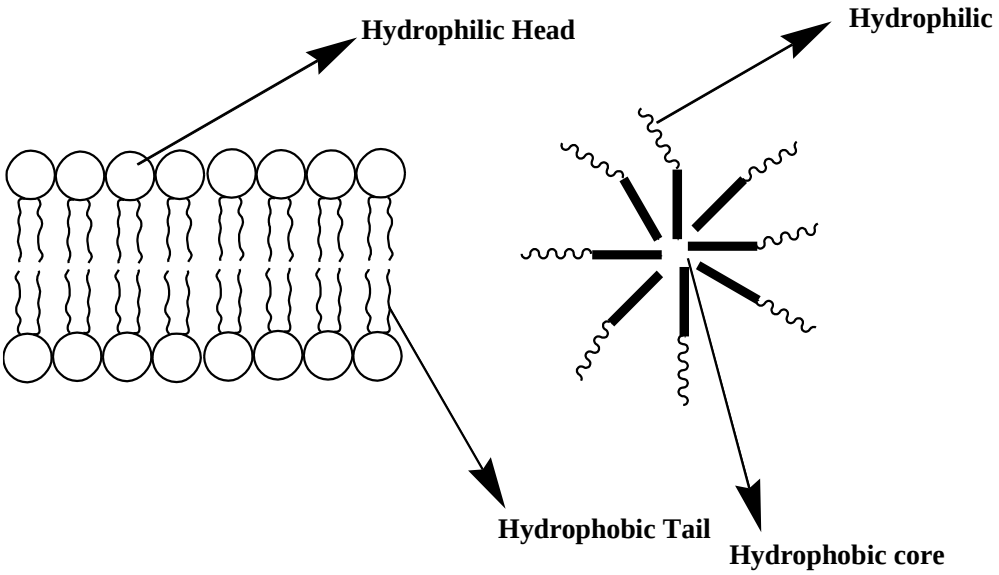

Figure 9-1: Micelle Formation

Types of Polymeric Micelles

The intermolecular forces that separate the core segment from the aqueous environment utilized to classify polymeric micelles. They are divided into three categories.

1. **Conventional micelles**

The core and shell interact hydrophobically in the aqueous environment, creating micelles. Poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide)-b-poly(ethylene oxide)-b-poly(ethylene oxide)-b-poly((ethylene oxide).

2. **Polyion complex micelles (PICMs)**

Electrostatic and Vander Waals interactions govern the structure and size of the charged micelles coronas. Polyion complex micelles have a simple synthesis approach, a high drug loading capacity, structural stability, prolonged circulation in the blood, and self-assembly in the aqueous medium, to name a few characteristics. Micelles are made in an aqueous medium without the use of an organic solvent. This will eliminate any potential harmful effects from the remaining organic solvent.

3. **Non-covalently connected polymeric micelles**

Polymeric micelles are formed in non-covalently connected polymeric micelles without the use of a block copolymer, with interpolymer hydrogen bonding complexation. Because of hydrogen bonding interactions, non-covalently connected polymeric micelles feature a core and a corona that is non-covalently joined at the homopolymer chain end.

Methods of Preparation

Direct dissolution method in an aqueous solvent, the block copolymer and medication are mixed. It's a term that's widely used to describe hydrophobic copolymers like poloxamers. The hydrophobic component of the block copolymer produces the core of micelles, while the hydrophilic portion forms the shell (Figure 9-1). Micelles of amphiphilic copolymers with low CMC values are frequently more stable in the medium, even at low amphiphile concentrations. The CMC is lowered by enhancing the copolymer's hydrophobicity, which enhances micelle stability. Solvent evaporation method Both copolymers and medicines are dissolved in this process using volatile organic solvents. Micelles are created by heating the core-producing

segments and dehydrating them. Micelles are formed by dissolving the copolymer and drug in separate aqueous solvents and then combining the two solutions. Water is added to the aforementioned film to create drug-loaded polymeric micelles. Dialysis procedure The medications in the copolymer are combined in an organic solvent before being placed in a dialysis bag. A dialysis bag is placed in a beaker filled with water. This solution, like the water, is continuously in and out. For proper drug loading, the dialysis process takes more than 36 hours.

Drug Targeting of Polymeric Micelles

Passive targeting of Polymeric Micelles The tumor microenvironment is used for passive targeting of nanocarriers such as polymeric micelles. The EPR effect plays a major role in their buildup (Maeda et al., 2000). Tumor vasculature expands abnormally to satisfy the expanding tumor's rising nutritional and oxygen demands, resulting in endothelial cells that are poorly aligned (Jain, 1987; Folkman, 1995; Roberts and Palade, 1997; Hobbs et al., 1998). The tumor blood arteries become highly permeable and the generation of vascular permeability factors such as nitric oxide, bradykinin, matrix metalloproteinases (MMPs), and vascular endothelial growth factor (VEGF) (Wu et al., 1998; Fang et al., 2011). The expanding tumor cells also compress lymph arteries, causing them to collapse, especially in the core area of the tumor, resulting in inadequate lymphatic drainage (Padera et al., 2004; (Maeda et al., 2000; Iyer et al., 2006).

Active Targeting of Polymeric Micelles Tumor cells and/or tumor vasculature frequently exhibit higher levels of particular molecules (antigens or receptors) that are not expressed or present at low levels on the surface of normal cells and tissues (Park et al., 2008; Kamaly et al., 2012). Active targeting takes advantage of this property of cancer cells to allow anti-cancer medicines to accumulate selectively in tumor tissue, tumor cells, or internal organelles of the cell (Nie et al., 2007). By chemically altering the surface of polymeric micelles have a high selectivity for antigens overexpressed on cancer cells, (Torchilin, 2007; Park et al., 2008; Torchilin, 2001, 2007). Actively targeted polymeric micelles reduce therapeutic side effects (Park et al., 2008; Danhier et al., 2010). Intracellular delivery of macromolecules like as DNA, siRNA, and proteins is aided by active targeting. Actively targeted delivery vehicles' anti-tumor efficacy stems (Kirpotin et al., 2006).

Defining the Concept of Multifunctionality

The preceding sections discuss targeting strategies and modifications of polymeric micelles, including very basic modifications for longevity, which are important for passive targeting of therapeutics solubilized within micelles, surface modification with ligands to allow for selective targeting as well as intracellular delivery of drugs and nucleic acids, and finally modifications that allow micelles to respond to a variety of intrinsic and extrinsic stimuli. While polymeric micelles allow for individual alterations, they also provide a platform for the integration of many components within a single micelle. Micelles can thus be engineered to contain two or more distinct alterations, allowing them to perform crucial therapeutic and diagnostic roles simultaneously or sequentially (Torchilin, 2006). The key to creating multifunctional micelles is to make sure that all of the components work together in a coordinated manner, such that the sum of their contributions is more than the sum of their contributions. It's like a symphony orchestra, where each instrument must be performed in perfect harmony to make a beautiful piece. Chemotherapy is difficult because cancer is a complicated illness with genetic and phenotypic variability within and between tumor types. Despite the development of molecularly targeted medicines, a subset of tumor cells may still evade the targeted route, leading to adaptive resistance and therapy failure (Blanco et al., 2009). It follows from the discussion above that using a multi-faceted approach for targeting cancer seems imperative. Much of current research has been directed toward such multifunctional micelles due to their evident

benefits in improving the effectiveness and optimising the safety and specificity of present and innovative chemotherapy regimens. Drug and Nucleic Acid Delivery Using Multifunctional Polymeric Micelles Drug and nucleic acid delivery using multifunctional polymeric micelles has been extensively investigated in recent years. A number of intriguing drug-loaded multifunctional polymeric micelle combinations have been studied, with a few of them being discussed below. Multifunctional micelles made of PLGA-PEG block copolymers have been described for the combination administration of DOX and PTX (Duong and Yung, 2013). PLGA-PEG was modified with a cell-penetrating moiety (TAT) and a specific ligand to boost the therapeutic impact of the medication combination over the solo therapies (folate). In KB cells (mouth epidermal carcinoma), the researchers studied single and dual drug-loaded micelles modified with folate or both TAT and folate ligands and observed that dual drug-loaded micelles modified with both ligands had a substantially lower IC50 value than single drug-loaded micelles. Although both approaches (co-delivery of two single drug-loaded micelles and dual drug-loaded micelles) showed a synergistic effect, the authors postulated that the drug ratio had a role. Magnetic nanoparticles are usually embedded in the core of MRI-responsive micelles, but Li et al. developed hybrid micelles made of Pluronic F127 and a peptide-amphiphile (PA) made of segments of a palmitic part, aspartic acid residue, and three histidine residues (pal-AAAAHHHD), in which the magnetic nanoparticles were embedded in the shell (Li et al., 2013f). In vitro and in vivo, the DOX-loaded hybrid micelles were effective T2 weighted MRI contrast agents, with the added benefit of a straightforward, convenient, and "green" production without the use of organic solvents (Li et al., 2013).

CONCLUSION

In this chapter, we show the versatility of this approach by investigating the development of the CMC of the same surfactant in several complicated electrolytic solutions, as previously described J. Chromatogr.A, (1995) developed a theoretical approach to determining the critical micelle concentration (CMC) using capillary electrophoresis and confirmed it by determining the CMC of sodium dodecyl sulphate in a simple electrolyte. The critical micelle concentration (CMC) in surfactant solutions was measured using an optical fibre. The detection of CMC is based on an adsorption effect in sample solutions containing sodium dodecyl benzenesulfonate. An incident beam was reflected at the interface between the fibre core and the solution, moving through the sensing zone alongside the fibre with recurrent reflections. Changes in adsorption circumstances alter the refractive index at the core's surrounding surface. The output signal at the CMC quickly rises due to the reflectivity shift induced by surfactant molecules adsorbing onto the surface of the fibre core. The two types of fibre are plastic cladding silica fibre (PCS) with a silica glass core and plastic optical fibre (POF) with a glass core.

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CHAPTER X

LIPOSOMES IN ALZHEIMER'S DISEASE: CURRENT STATE AND FUTURE DIRECTIONS

ABSTRACT

Liposomes are nanosized vesicles composed of phospholipid bilayers that can encapsulate various drugs and deliver them to the targeted site. The unique composition of liposomes enables encapsulation of both hydrophilic and hydrophobic drugs, resulting in improved pharmacokinetics, reduced toxicity, and increased efficacy compared to free drugs. Liposomes offer several advantages over conventional drug delivery systems, such as enhanced solubility, stability, biocompatibility, and specificity. In Alzheimer's disease (AD) liposomes offer several advantages, including targeted drug delivery, enhanced permeability and retention (EPR) effect, and controlled drug release. This chapter provides a comprehensive overview of the current state and future directions of liposome-based. It covers the methods and techniques for preparing and characterizing liposomes with different properties and functions, the strategies for achieving active and passive targeting of liposomes to AD, the applications of liposome-based drugs for different types of cancer therapy, and the emerging trends and opportunities for improving the efficacy and safety of liposome-based cancer therapy. The chapter also discusses the potential barriers and solutions for translating liposome-based Alzheimer's disease from laboratory to clinic.

Keywords: Liposomes, Alzheimer's disease, FDA- approved, Targeting, enhanced permeability

INTRODUCTION

Alzheimer's disease (AD) is a complex condition that results in the deterioration of cognitive cells and is primarily responsible for dementia, a loss of mental capacity and self-reliance in daily tasks. The disease is believed to have two main causes, namely cholinergic and amyloid, and is influenced by several risk factors including aging, genetic predisposition, head injury, vascular diseases, contamination, and environmental factors. Currently, there are only two drugs available to treat AD, namely cholinesterase enzyme inhibitors and N-methyl d-aspartate (NMDA) antagonists. However, both drugs only provide limited relief for the symptoms of AD, without addressing its root causes or offering a cure. In the current effort to develop effective treatments that can decelerate or modify the progression of AD, research is presently focused on comprehending the pathology of AD through examination of various mechanisms such as irregular tau protein metabolism, -amyloid, inflammatory response, and cholinergic and free radical damage. This chapter will cover the drugs that are currently available in the market as well as potential alternatives for novel AD therapies such as disease-modifying therapeutics (DMT), chaperones, and natural compounds. The pharmacokinetic and pharmacodynamic characteristics of different AChEIs exhibit variation. Liposomes is used for formation of controlled and targeted drug delivery system to targeting the cancerous cells. However, the adoption of liposomes has been slow due to their classification as "novel" by regulators, even when prepared using compendial excipients. Liposomes can help overcome formulation challenges by enhancing the performance and processability of resulting materials. Liposomes analysis includes clinical indications for gene treatments, metabolic and infectious disorders, cancer, dental and ophthalmic conditions, and other conditions. The use of liposomes is aimed at enhancing the functionality of the pharmacological product, according to Gomes. An increasing number of new APIs have been discovered due to advancements in high-throughput screening technology. However, approximately 75% of novel drug candidates suffer from poor aqueous solubility and inadequate bioavailability, which can be attributed to the growing structural complexity of therapeutic prospects. To overcome this challenge, various tried-and-

tested as well as cutting-edge approaches, such as cyclodextrin inclusion, microemulsion, nanocrystals, cocrystals, and amorphous dispersions, are utilized to enhance the delivery of class IV pharmaceuticals compounds. Among these approaches, amorphization of pharmaceuticals has emerged as one of the most successful methods for increasing solubility and dissolution, thereby improving therapeutic bioavailability. Amorphous solids have higher internal energy than their crystalline counterparts and lack long-range order in molecular packing. To stabilize amorphous materials and improve their oral bioavailability, polymer-based amorphous solid dispersions have been widely employed. Additionally, high-dose medication formulations may encounter issues due to the larger end product volume. Despite these limitations, pharmaceutical companies still prefer direct compression (DC) as the most popular method. This machinery process involves a straightforward physical mixing of the active medicinal in liposomes. Liposomes used in the DC process must perform various functions, such as facilitating acceptable excellent binding capacity, to produce tablets effectively. However, finding a single material with all these desirable attributes is a challenging task. AD drugs as shown in table 10-1, .1, have a limited therapeutic window and a high potential for toxicity. A vast area of research is currently underway to comprehend the pathophysiology of AD and develop effective treatments. AD is a complex neurodegenerative disorder that progresses over time and is one of the leading causes of dementia worldwide. In the United States alone, approximately 5.3 million individuals are afflicted with AD, of which 5.1 million are aged 65 or older, while 200,000 have developed the disease at a younger age. According to reports, AD is characterized by histopathological features such as intracellular aggregations of neurofibrillary tangles (NFTs), which are composed of hyperphosphorylated microtubule-associated proteins, as well as extracellular aggregates of plaques. Tangle formation is caused by the accumulation of A in the locus coeruleus, trans entorhinal, and entorhinal regions of the brain

Table 10.1. Types of FDA approved drugs used in the treatment of cancer

Drug	**Target site**
Galantamine	mild-to-moderate
Rivastigmine	targeting the pair acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE)
Donepezil	AChE inhibitor
Memantine	mild-to-moderate dementia

Liposomes in AD Therapy

The term "liposome" alludes to its structural components, the phospholipids, rather than its size and it can be produced in a variety of sizes using either unilamellar or multilamellar assembly. The material used to create a cell membrane is used to create a microscopic bubble (vesicle), as shown in Figure 10-2. Utilizing liposomes that have been drug-loaded, medications for cancer and other conditions can be delivered. The basic constituents of membranes are usually phospholipids, which are molecules with head and tail groups. The tail, which is composed of long chains of hydrocarbons, is repelled by water, but the head, which is formed of hydrocarbons, is attracted to it. Stable, two-layer membranes contain phospholipids. The heads are drawn to water when it is present and form a surface that faces the water. Since water repels them, the tails align to produce a surface far from the water. One layer of the head is pulled to the water in the vicinity and confronts the cell's exterior.

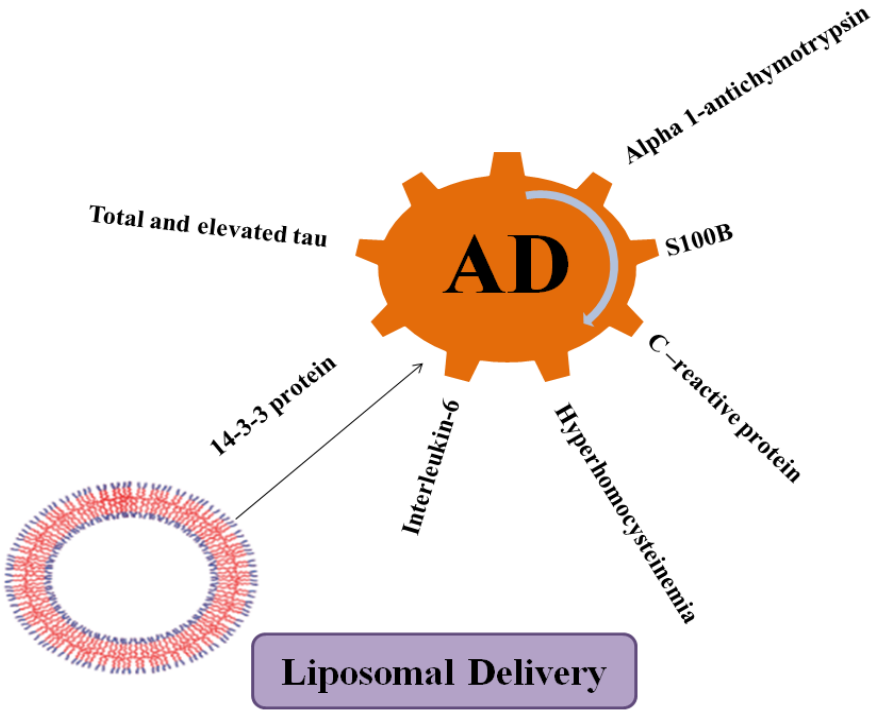

Figure 10-2: Due to a surface coating of a polymer, typically a lipid derivative of polyethylene glycol (PEG), shows the targeting delivery of AD

Different pathways to targeted site for the management of AD

Liposomes play a targeted role in the targeted delivery of formulation for the management of AD. Signal transduction pathways play a critical role in the targeted delivery of drugs for AD of the management using API. These pathways are the series of chemical reactions that occur inside cells in response to extracellular signals, leading to changes in gene expression, protein activity, and cellular behavior. These strategies offer the potential to enhance drug efficacy and reduce toxicity, providing a promising approach for the development of more effective and less harmful AD therapies.

AGEs RAGEs Pathways

The overexpression of the receptor for advanced glycation endproducts (RAGE) in many types of AD development and progression. Moreover, RAGE can activate signaling passage such as PI3K/AKT, MAPK/ERK, and NF-κB, which can promote AD. Targeting RAGE using small molecule inhibitors, antibodies, or RAGE decoy receptors has shown promising results in preclinical studies, and clinical trials are currently underway to evaluate their efficacy in AD treatments.

Transforming growth factor-beta (TGF-β) pathway

The TGF- pathway with liposomes has significant implications in the emergence of AD, manifesting in two distinct ways. In the initial stages, TGF- triggers apoptosis and limits cell development, thereby preventing AD.

Epidermal growth factor receptor (EGFR) pathway

New treatments for lung cancer using liposomes molecules and the expanding area of targeted AD medicines using liposomes have the potential to greatly benefit from the discovery and clinical use of inhibitors that target EGFR. The key signaling pathways activated by EGFR receptors are PI3 kinase, Ras-Raf-MAPK, JNK, and PLC, which have a wide range of biological effects.

Wnt/β-catenin signaling pathway

The Wnt/β-catenin signaling pathway is a complex and essential cellular communication pathway that plays a significant role in various biological processes, including embryonic development, tissue homeostasis, and cell proliferation. Dysregulation of this pathway has been implicated in several diseases, including cancer and neurodegenerative disorders like Alzheimer's disease (AD). In Alzheimer's disease, there is growing evidence suggesting that the Wnt/β-catenin signaling pathway may be involved in the pathogenesis of the disease. Here's a simplified explanation of how this pathway might be related to AD:

Amyloid Beta (Aβ) Plaques: One of the hallmark features of AD is the accumulation of amyloid beta (Aβ) plaques in the brain. Aβ is derived from a larger protein called amyloid precursor protein (APP). Wnt signaling has been suggested to influence the processing of APP. Activation of the Wnt/β-catenin pathway has been proposed to decrease the production of Aβ through modulation of enzymes involved in APP processing.

Neuroinflammation and Microglia Activation: Chronic neuroinflammation and activation of microglia (the brain's immune cells) are observed in AD. Wnt signaling has been linked to the regulation of inflammation. Activation of the Wnt/β-catenin pathway might play a role in controlling microglia activation and inflammation in the brain.

Neuronal Function and Survival: Wnt signaling is crucial for the development and maintenance of neurons. In AD, there is extensive loss of neurons, which contributes to cognitive decline. Activation of the Wnt pathway could potentially promote neuronal survival and function.

Tau Pathology: Another hallmark of AD is the accumulation of abnormal tau protein in neurofibrillary tangles. Wnt/β-catenin signaling might influence tau phosphorylation and aggregation.

Synaptic Plasticity: Wnt/β-catenin pathway is also associated with synaptic plasticity, which underlies learning and memory. Impaired synaptic plasticity is a characteristic of AD.

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ABOUT THE BOOK

This book consists of ten chapters that comprehensively explore Alzheimer's disease and potential therapeutic strategies. Chapter 1 analyzes molecular pathways related to Alzheimer's and cognitive impairment, emphasizing the APOE gene's role. Chapter 2 discusses dendrimer optimization for enhanced drug delivery. Chapter 3 introduces Ursolic Acid as a potential anti-Alzheimer's agent. Chapter 4 explores dendrimers as neuroprotective agents. Chapter 5 highlights the Mevalonate pathway for Alzheimer's treatment. Chapter 6 covers green-synthesized silver nanoparticles and their biomedical applications. Chapter 7 focuses on proliposomes' advantages over liposomes in drug delivery. Chapter 8 delves into carbon nanotubes for smart drug delivery. Chapter 9 discusses polymeric micelles in drug targeting. Finally, Chapter 10 explores liposomes in Alzheimer's therapy, offering a comprehensive overview of advanced drug delivery methods in the context of Alzheimer's disease treatment.

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