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CURCUMIN LOADED FLEXIBLE DENDRIMERS FOR INTRANASAL DELIVERY: A PROMISING APPROACH FOR THE MANAGEMENT OF COGNITIVE/ NEURODEGENERATIVE DISORDERS

Ganesh N. S., Navya V.*, J. Adlin Jino Nesalin

[1]Department of Pharmaceutics, T. John College of Pharmacy, Bengaluru, Karnataka, India.

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***Corresponding Author**

Navya V.

Department of Pharmaceutics, T. John College of Pharmacy, Bengaluru, Karnataka, India.

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ABSTRACT

The present study was aimed at the formulation, optimization, and evaluation of Curcumin loaded PAMAM dendrimer for cognitive/ neurodegenerative disorders by intranasal route. Curcumin, a BCS Class IV drug, suffers from limited solubility and permeability, restricting its therapeutic efficiency. To overcome this drawback, Dendrimers the radially symmetric molecules with well defined tree-like arms or branches are selected as carrier. Dendrimers were synthesized by using divergent method and later Curcumin was loaded. Design of study involves variables such as different generations of PAMAM dendrimers, at various dendrimer and curcumin ratios. In this study a total of 6 formulations were formulated at various ratios using different generations i.e., G3 and G4. The optimized formulation exhibited an entrapment efficiency of 80%. *In-vitro* diffusion studies of the optimized formulation showed 42% release at the end of 8th h. Based on the release kinetics the optimized formulation exhibited Super Case II Transport. The optimized formulation was formulated as nasal drops.

KEYWORDS: PAMAM Dendrimers, Curcumin, divergent method.

1. INTRODUCTION

Neurodegenerative diseases (NDs) are chronic, progressive disorders characterized by the loss or dysfunction of neurons in the brain or peripheral nervous system. Common examples

include Alzheimer's disease, Parkinson's disease, and multiple sclerosis. They can cause motor, cognitive, and psychiatric problems and are often associated with abnormal protein accumulation and aging. A major challenge in treating NDs is the blood–brain barrier (BBB), which limits the delivery of drugs into the brain. Although several treatments are available, most mainly manage symptoms rather than halt disease progression. Limited drug delivery, adverse effects, and the complex nature of neuronal degeneration make effective treatment difficult.[1] Neurodegenerative diseases (NDs) have complex and poorly understood disease mechanisms, making effective treatment difficult. Understanding their cellular and molecular pathways is essential for developing new therapeutic strategies and improving patient survival and quality of life sex differences are also observed: Parkinson's disease is more common in men, while Alzheimer's disease is more common in women. Women with Parkinson's may experience faster disease progression, whereas men more frequently develop motor symptoms and REM sleep behaviour disorder.[2]

Curcumin, a hydrophobic polyphenol derived from Curcuma longa (turmeric), has anti-inflammatory, antioxidant, immunomodulatory, neuroprotective, anticancer, and antibacterial properties. It shows potential in treating neurodegenerative diseases such as Parkinson's, Alzheimer's, Huntington's disease, ALS, and prion diseases. However, its clinical use is limited by poor water solubility, low bioavailability, rapid metabolism, poor blood stability, and limited ability to cross the blood–brain barrier (BBB).[5] Curcumin has significant neuroprotective effects. It may improve cognitive and motor functions, reduce oxidative stress (MDA), enhance antioxidant defences (SOD and GSH), and decrease pro-inflammatory cytokines in brain tissue.[6] Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease characterized by damage to myelin in the brain and spinal cord. This disrupts nerve signaling and can cause fatigue, vision problems, muscle weakness, spasms, poor coordination, and bladder dysfunction. Inflammation leads to demyelination, impaired remyelination, axonal damage, and neuronal death. MS may occur in relapsing or progressive forms. Genetic, environmental, autoimmune, and infectious factors such as Epstein–Barr virus may contribute to its development. Although there is no cure, available treatments can manage symptoms and slow disease progression.[8]

Dendrimers are nanosized, highly branched, globular macromolecules widely used as drug-delivery carriers. Their unique, monodispersed structure allows drugs to be loaded through electrostatic interactions or covalent conjugation. They consist of a central core, repeated

generations, and surface functional groups. For example, G5 PAMAM dendrimers are about 5.5 nm in diameter, similar to hemoglobin. Their surface charge affects biocompatibility. Neutral and negatively charged dendrimers generally show lower haemolysis, whereas positively charged dendrimers can disrupt negatively charged cell membranes, causing cell lysis and reduced biocompatibility.[10] Surface functionalization, such as PEGylation, can improve dendrimer performance by modifying zeta potential, blood circulation time, and in-vivo distribution. Dendrimers are also promising gene-delivery carriers because cationic dendrimers can form stable dendriplexes with negatively charged nucleic acids through electrostatic interactions. Polyamidoamine (PAMAM) dendrimers consist of a central core, amide-containing branches, and peripheral amine groups. Their internal cavities and surface functional groups can be modified to encapsulate and deliver drugs or other therapeutic agents. PAMAM dendrimers have potential applications in drug delivery, antibacterial and antiviral therapy, cancer treatment, antioxidant delivery, diagnosis, and targeted therapy. However, their cytotoxicity, particularly in positively charged PAMAM dendrimers, depends on concentration and surface properties. PEGylation can reduce this toxicity and improve their biocompatibility. G5 and lower-generation PAMAM dendrimers are generally considered relatively safe.[11]

The blood–brain barrier (BBB) is a major obstacle to CNS drug delivery because its tight junctions, low transcytosis, efflux pumps, and enzymes prevent most drugs from entering the brain. Generally, molecules that are small (<400 Da), non-polar, and less complex cross more readily; about 98% of drug molecules do not reach the brain at therapeutic concentrations.[12,13] The nose-to-brain route is an alternative delivery pathway that can bypass the BBB. Drugs can reach the brain through the olfactory and trigeminal nerve pathways, with the olfactory route providing access to the olfactory bulb and the trigeminal pathway providing access to deeper brain regions. Nasal nanoparticles have been detected in the olfactory bulb within minutes of administration.[14] Major advantages include direct brain delivery and potentially reduced systemic exposure and peripheral side effects. A landmark 2002 human study showed that intranasally administered insulin, melanocortin, and vasopressin could reach the cerebrospinal fluid within minutes, supporting the potential of nose-to-brain drug delivery.[16]

In this context, the present study was undertaken to develop, formulate and evaluate Curcumin loaded PAMAM dendrimer for management of Neurodegenerative disorder

through intranasal delivery.

2. MATERIALS AND METHODS

Curcumin was used as an API, Ethylenediamine was used as come molecule and amidation reagent in synthesis of PAMAM dendrimer, Methyl acrylate was used as a Michael addition reagent in dendrimer synthesis, Methanol was used as a solvent.

2.1. Preparation of curcumin loaded PAMAM-dendrimers

PAMAM dendrimers were synthesized by divergent method starting with a core "initiator" molecule which contains functional groups capable of acting as active sites in the initial reaction. Outward growth of PAMAM dendrimers was accomplished by alternating between two reactions: Michael addition of the amino-terminated surface onto methyl acrylate, resulting in an ester-terminated outer layer and coupling with ethylene diamine to achieve a new amino-terminated surface**.**

Synthesis of ester-terminated (half-generation) PAMAM dendrimers

Ethylene diamine (EDA) in the very first step was dissolved in methanol, cooling the mixture in an ice bath. Then methyl acrylate was added dropwise at stirring to the dendrimer solution. The mixture was kept at room temperature.

Synthesis of amino-terminated (full-generation) PAMAM dendrimers

EDA and multi-ester were dissolved in methanol separately and then EDA solution was gradually added to the cold multi-ester solution. After the addition was completed, the mixture was allowed to warm at room temperature. These steps were repeated to synthesize G3 and G4 PAMAM Dendrimers.

Encapsulation of Curcumin within PAMAM Dendrimers

10 mg of Curcumin was first dissolved in ethanol, and the dendrimer was separately solubilized in PBS; the two solutions were then mixed together under gentle stirring to allow curcumin to encapsulate within the dendrimer.

Experimental Design

Curcumin loaded PAMAM dendrimers were prepared by varying the concentrations and generations of PAMAM dendrimers.

Table 1: Formulation of Curcumin loaded PAMAM dendrimers.

FORMULATION	DRUG	DENDRIMER
F1	10mg	G3 10mg
F2	10mg	G3 20mg
F3	10mg	G4 10mg
F4	10mg	G4 20mg
F5	10mg	G3 5mg+ G4 5mg
F6	10mg	G3 10mg+ G4 10mg

2.2. Evaluation of curcumin loaded dendrimers

2.2.1. Percentage entrapment efficiency

The entrapment efficiency of curcumin loaded dendrimers was determined to evaluate the amount of drug successfully entrapped by the dendrimer. A 10 mL aliquot of the dendrimer suspension was centrifuged at 10,000 rpm for 30 minutes to separate the unentrapped (free) drug from the vesicular fraction. The clear supernatant containing the free drug was carefully collected and analysed using a UV Visible spectrophotometer at 425 nm. The amount of Curcumin entrapped within the dendrimers was calculated by subtracting the concentration of free drug in the supernatant from the total drug initially added to formulation.

The percentage entrapment efficiency (%EE) was calculated using the formula:

$$\textbf{\% Entrapment Efficiency} = \frac{(Practical\ drug\ loading)}{(Theoretical\ drug\ loading)} \times 100$$

2.2.2. *In vitro* drug release

In vitro drug release of Curcumin loaded dendrimers was evaluated using a Franz diffusion cell with phosphate buffer (pH 6.0) as the receptor medium. A biological membrane was mounted between the donor and receptor compartments, and the required quantity of Curcumin loaded dendrimer formulation was applied on the membrane surface. At predetermined time intervals, 1 mL of sample was withdrawn from the receptor compartment and immediately replaced with an equal volume of fresh buffer to maintain sink conditions. The receptor medium was continuously stirred using a magnetic stirrer to minimize boundary layer effects. The samples were analysed using a UV Visible spectrophotometer, and the cumulative percentage drug release was calculated. *In vitro* drug release study.

2.2.3. Surface morphology study

Scanning electron microscopy (SEM) was performed to examine the particle size and surface morphology (Fig. 1).

2.2.4. Kinetic modelling

In order to understand the kinetic and mechanism of drug release, the result of in vitro drug release study of nanoparticles were fitted with various kinetic equation like zero order (cumulative % release vs. time), first order (log % drug remaining vs. time), Higuchi's model (cumulative % drug release vs. square root of time), Peppas plot (log of cumulative % drug release vs. log time). R2 and k values were calculated for the linear curve obtained by regression analysis of the above plots (Table 2).

2.3. Evaluation of Curcumin loaded dendrimer nasal drops

2.3.1. Percentage entrapment efficiency

The entrapment efficiency of curcumin loaded dendrimers nasal drops was determined to evaluate the amount of drug successfully entrapped by the dendrimer. A 10 mL aliquot of the dendrimer suspension was centrifuged at 10,000 rpm for 30 minutes to separate the unentrapped (free) drug from the vesicular fraction. The clear supernatant containing the free drug was carefully collected and analysed using a UV Visible spectrophotometer at 425 nm. The amount of Curcumin entrapped within the dendrimers was calculated by subtracting the concentration of free drug in the supernatant from the total drug initially added to formulation.

The percentage entrapment efficiency (%EE) was calculated using the formula:

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3. RESULTS AND DISCUSSION

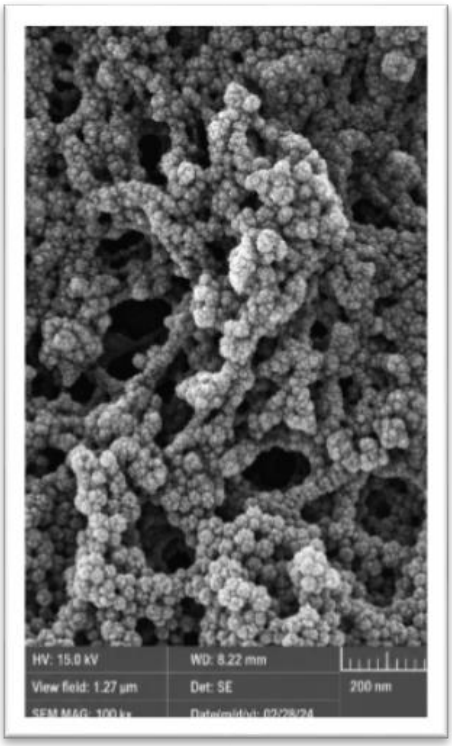


Fig. 1: SEM of Curcumin loaded dendrimer.

The Curcumin loaded PAMAM dendrimer was prepared using divergent method. Total 6 formulations were formulated at various ratios using various generations as shown in table 1.

Table 2: Correlation coefficients according to different kinetic equations.

Formulation	% Cumulative drug release	Zero order	First order	Higuchi plot	Peppas plot
F1	59%	0.9954	0.7093	0.9342	0.7271
F2	51%	0.9939	0.7987	0.8918	0.8201
F3	45.2%	0.9953	0.8138	0.8917	0.8327
F4	37.9%	0.9974	0.8243	0.9018	0.8505
F5	53.2%	0.9942	0.7852	0.8919	0.7975
F6	42.5%	0.9978	0.7777	0.9227	0.804

The average entrapment efficiency (%) of Curcumin loaded dendrimers were found to be 60%, 70%, 67%, 76%, 73%, and 80% in formulations F1, F2, F3, F4, F5, and F6 respectively. The maximum entrapment efficiency was observed in formulation F5.

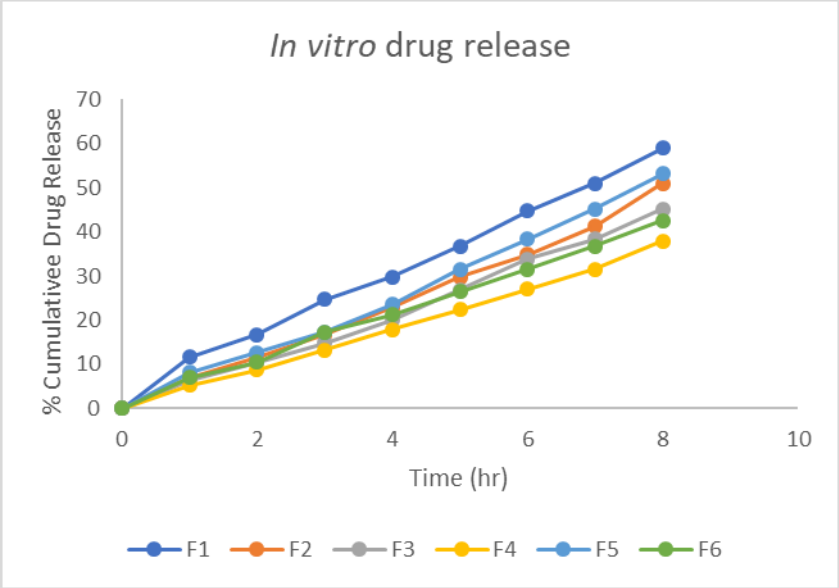


Fig. 2: Cumulative percentage drug release profile of Curcumin.

The *In vitro* drug release data of Curcumin loaded dendrimers (F1-F6) were analysed using various kinetic models as illustrated in (Table 2). The cumulative percentage drug release data of Curcumin loaded dendrimers F1, F2, F3, F4, F5, and F6 after 8 hrs were found to be 59%, 51%, 45.2%, 37.9%, 53.2%, and 42.5% respectively, and are shown in Table 2. Among these formulation F6 was selected as ideal formulation.

Table 3: Regression co-efficient (r^2) values of different kinetic models and diffusion exponent (n) of Peppas model of Nasal drops of Curcumin loaded dendrimers.

Formulation	Zero order	First order	Higuchi plot	Peppas plot	'n' values
Nasal drops	0.9964	0.781	0.9288	0.8194	0.93

Calculated regression co-efficient values of different kinetic models are tabulated in table 3. The Peppas model is widely used to confirm the release mechanism. Then 'n' value was found to be 0.93. This indicates that the release approximates Super Case Ⅱ Transport mechanism which indicates the release mechanisms are driven by polymer matrix erosion and swelling, accelerating the release rate.

CONCLUSION

Curcumin loaded PAMAM dendrimers were optimized and formulated as a nasal drop to overcome poor bioavailability.

Based on the experimental results, it can be concluded that, the pre-formulation studies involving solubility, melting point, λ-max determination, FT-IR spectrum, and DSC investigation were found to be comparable with the standard values, confirming the identity and purity of the drug. PAMAM dendrimers G3 and G4 were successfully synthesized using divergent method. Curcumin loaded dendrimers were successfully prepared using different combinations of dendrimers. Among different drug dendrimer ratios, formula F6 showed maximum % entrapment efficiency, which was found to be 80%. Formulation F6 showed *In vitro* cumulative drug release of 42.5% at the end of 8th hour. Based on % entrapment efficiency and % cumulative drug release F6 was selected as ideal formulation. The F6 formulation was taken into consideration and formulated as nasal drops. The optimized curcumin loaded dendrimer nasal drops showed % entrapment efficiency of 79%, %Cumulative drug release of 41.89% at the end of 8th hour, and diffusion exponent (n) of 0.93.

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