Retrospective Quality-By-Design Optimization of Memantine-Loaded Pegylated Plga Liposomal Formulation for Enhanced Nose-To-Brain Delivery in Alzheimer's Disease

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ABSTRACT

Background: Alzhimer's Disease is one of the major neurodegenerative disorders where there is limited efficacy of therapeutic drug action, primarily because of the lack of gene transfer across the blood–brain barrier. Nanocarrier-based delivery systems capable of targeting the brain following intranasal administration are under investigation for the improvement of brain targeting of anti-Alzheimer drugs. To find the optimal formulation for carrying memantine in PEGylated PLGA liposomal nanoparticles towards nasal–brain delivery, the present study was designed in a retro view manner employing the Quality by Design (QbD).

Materials and methods: In order to formulate memantine loaded- PEGylated PLGA liposomes, a modified solvent evaporation and thin-film ($ март as per previously mentioned technique. Memantine-loaded-PEGylated PLGA liposomes were prepared by modification of solvent evaporation and thin-film ($ март technique. The particle size, zeta potential, polydispersity index, entrapment efficiency, in vitro drug release, ex vivo nasal permeation and stability were measured. The formulation optimization has been done by applying the principle of retrospective QbD and by using statistical assessment.

Results: The optimized formulation gave the particle size of 156.2 ± 3.9 nm, polydispersity index of 0.184 ± 0.01, zeta potential of −29.4 ± 1.5 mV and entrapment efficiency of 89.8 ± 1.9%. The Higuchi diffusion kinetic model showed sustained release of drug to the greater extent of 91.8 ± 3.2% after 24 hours. Ex vivo permeation studies revealed that the permeation flux and nasal tissue retention were significantly better than pure memantine solution ($p < 0.001$). The physicochemical stability was acceptable with no significant aggregation or leakage of the drug throughout the study period as observed in the stability analysis.

Conclusion: The optimized formulation gave the particle size of 156.2 ± 3.9 nm, polydispersity index of 0.184 ± 0.01, zeta potential of −29.4 ± 1.5 mV and entrapment efficiency of 89.8 ± 1.9%. The Higuchi diffusion kinetic model showed sustained release of drug to the greater extent of 91.8 ± 3.2% after 24 hours. Ex vivo permeation studies revealed that the permeation flux and nasal tissue retention were significantly better than pure memantine solution ($p < 0.001$). The physicochemical stability was acceptable with no significant aggregation or leakage of the drug throughout the study period as observed in the stability analysis.

Keywords: Alzheimer's disease, PEGylated PLGA liposomes, Nose-to-brain delivery, Nanoparticles, Intranasal drug delivery.

INTRODUCTION

Alzheimer's disease is a type of dementia, the most common, and a significant public health problem with progressive cognitive decline and neuronal degeneration, β-amyloid plaque formation, and neurofibrillary tangles.[1] Although there has been significant progress in neuropharmacology, the treatment of Alzheimer's disease has been limited by the failure of numerous drug therapies to successfully cross the blood–brain barrier (BBB), and so gain access to the central nervous system (CNS).[2] A number of oral pharmacotherapeutic drugs that are used to treat Alzheimer's disease are typically poorly bioavailable in the brain and prone to high first-pass hepatic metabolism, systemic side-effects, and low therapeutic efficiency.[3]

Memantine is a neuroprotective agent, a modulator of N-methyl-D-aspartate (NMDA) receptors, that is being widely prescribed for moderate and severe forms of Alzheimer's disease because of its effect on preventing glutamate-mediated excitotoxicity.[4] However, oral administration of memantine has its drawbacks including reduced CNS bioavailability, peripheral side effects, and variable bioavailability such that other delivery systems that could improve CNS bioavailability would be desirable.[5]

Intranasal or nose-to-brain delivery is one of the new methods that has attracted much interest within recent years as a non-invasive route that avoids the BBB by using the olfactory and trigeminal neural pathways.[6] This way of delivery allows the therapeutic molecules to be delivered directly into the brain which prevents that therapeutic molecules are delivered into the blood stream or are metabolised in the liver causing the first step of metabolism.[7] In recent years, studies have shown that nanoparticulate and liposomal systems are able to significantly enhance intranasal drug transport and retention in the CNS.[8]

The biodegradability, biocompatibility, and controlled release capability together with the capacity to encapsulate hydrophilic and lipophilic drugs make poly (lactic-co-glycolic acid) (PLGA) nanoparticles and liposome drug carriers very attractive strategies. The PEGylation process also enhances the stability of nanoparticles and their ability to penetrate mucus, circulate in the bloodstream, and withstand enzymatic degradation which enhance the efficiency of drug delivery through biological membranes.[10] Memantine-PEG-PLGA Nanoparticles have previously been shown to successfully target brain in experimental Alzheimer's models and decrease beta-amyloid load in the brain.[11]

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Likewise, liposomal formulations have shown superior therapeutic efficacy and lesser neurotoxicity in the studies related to the applications in CNS.[12]

Increasingly, Quality-by-Design (QbD) has become a manufacturing strategy focussed on achieving desired outcomes, risk analysis, critical quality attributes (CQAs) and process optimisation so as to obtain reproducible and robust formulations.[13] The use of QbD in nanoformulation development allows for optimizing factors such as particle size, entrapment efficiency, drug release behavior and formulation stability.[14]

While there have been several works on evaluation of intranasal delivery of nanoparticles-based systems for Alzheimer's disease, few are available concerning the optimization of PEGylated PLGA based liposomal systems using the QbD approach to improve NBD.

Hence, in the present study, a Quality-by-Design (QbD) approach was optimised and characterised to formulate a memantine-loaded PEGylated PLGA liposomal formulation for further maximisation of intranasal brain targeting potential and therapeutic benefit for Alzheimer's disease management.

MATERIALS AND METHODS

Materials: Memantine hydrochloride was purchased from a certified pharmaceutical supply company. Poly (lactic-co-glycolic acid) (PLGA) and other analytical-grade materials such as polyethylene glycol (PEG-2000) were purchased from standard commercial materials. Pharmaceutical or HPLC grade solvents and chemical were used for making the formulation and for analysis.

Retrospective Quality-by-Design (QbD) Based Formulation Design

A retrospective Quality-by-Design (QbD) approach was used to optimize the formulation of memantine loaded-PEGylated PLGA-liposomes for nose to brain administration. Critical Quality Attributes (CQAs) were determined by referring to the literature and the formulated objective.

These Critical Quality Attributes were particle size, polydispersity index, zeta potential, entrapment efficiency and in vitro drug release. Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) includingopolymer concentration, lipid ratio, PEG content, sonication time and stirring speed were evaluated in a systematic manner using the risk assessment tools and optimization principle.

Preparation of Memantine-Loaded PEGylated PLGA Liposomes

The preparation of Memantine-Loaded PEGylated PLGA liposomes was done by modified solvent evaporation and thin film hydration technique. In brief, Brandon was dissolved in an organic solvent mixture and phospholipids, cholesterol and PEG were also dissolved, and memantine was added. The amount of organic phase was removed by evaporation in a vacuum evaporator, and phosphate buffer was added to it under continuous stirring. So, a vesicular dispersion was obtained after sonication in order to get a uniform nanosuspension with smaller particle size.

The optimized formulations were kept at refrigerated conditions to be evaluated further.

Characterization and Statistical analysis

Optimized formulations have been characterized by particle size and polydispersity index, zeta potential, entrapment efficiency, morphology and in-vitro drug release profile by standard analytical technique.

The dialysis membrane diffusion method has been used to determine the drug release in phosphate buffer (pH 6.4). Each experiment was replicated three times and values obtained were presented as mean values ± S.D. The statistical analysis and optimization were conducted in Design-Expert® software and the p value is significant when < 0.05.

RESULTS

[Table 1] gives an overview of the optimized and physicochemical properties of the various experimental formulations. The optimised formulation F6 had the smallest particle size, minimum polydispersity index, most zeta stability and highest EE of all the batches prepared. In vitro drug release profile of the optimized memantine loaded PEGylated PLGA liposomal formulation is summarized in [Table 2] showing sustained and controlled release of drug from the formulation within 24 hrs. As revealed in [Table 3], the ex vivo parameters of permeation by nasal tissue showed the optimized formulation to possess higher permeation flux and higher nasal tissue retention as compared to pure memantine solution.

The optimized formulation was also found to be stable to storage as reflected by the minimal changes in particle size, zeta potential, and entrapment efficiency (EE) of optimized formulation with storage time. [Table 4]

In vitro drug release profile is shown in the [Figure 1], comparing two different formulations namely pure memantine and the optimized form, membrane as a sustained release formulation, showing the sustained release behavior observed for the membrane based nanoparticle system. [Figure 2] is taken from the comparative study of brain uptake efficiency of optimized formulation of memantine solution and non-PEGylated liposomes versus the non-PEGylated liposomes prepared using other liposomes with or without polymerized ethylene glycol.

Table 1: Optimization and Physicochemical Characteristics of Experimental Formulations

Formulation	Particle Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)
F1	242.6 ± 8.1	0.381 ± 0.02	-18.2 ± 1.3	61.4 ± 2.8
F2	221.4 ± 6.9	0.342 ± 0.03	-20.5 ± 1.1	66.7 ± 2.4
F3	198.3 ± 5.7	0.291 ± 0.02	-22.6 ± 1.4	71.5 ± 3.1
F4	184.7 ± 4.2	0.248 ± 0.01	-24.9 ± 1.6	78.3 ± 2.7
F5	171.8 ± 5.3	0.221 ± 0.02	-26.7 ± 1.2	82.6 ± 2.5
F6 (Optimized)	156.2 ± 3.9	0.184 ± 0.01	-29.4 ± 1.5	89.8 ± 1.9

Table 2: In Vitro Drug Release Kinetics of Optimized Formulation

Time (h)	Cumulative Drug Release (%)
1	18.4 ± 1.2
2	29.7 ± 1.6
4	42.9 ± 2.1
6	55.3 ± 2.5
8	64.1 ± 2.3
12	76.5 ± 2.7
24	91.8 ± 3.2

Table 3: Ex Vivo Nasal Permeation Parameters

Parameter	Pure Memantine Solution	Optimized PEGylated Liposomes	p value
Flux (µg/cm²/h)	48.7 ± 3.6	96.2 ± 4.8	<0.001
Permeability Coefficient (cm/h ×10⁻³)	2.11 ± 0.19	4.63 ± 0.31	<0.001
Drug Retention in Nasal Tissue (%)	31.4 ± 2.2	68.9 ± 3.7	<0.001

Table 4: Stability Profile of Optimized Formulation

Parameter	Initial	1 Month	3 Months
Particle Size (nm)	156.2 ± 3.9	160.8 ± 4.4	165.7 ± 5.1
Zeta Potential (mV)	-29.4 ± 1.5	-28.7 ± 1.6	-27.9 ± 1.8
Entrapment Efficiency (%)	89.8 ± 1.9	88.6 ± 2.1	86.9 ± 2.5

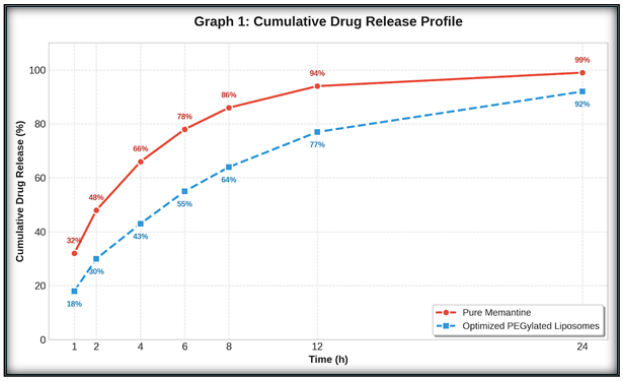


Figure 1: Drug Release Curve

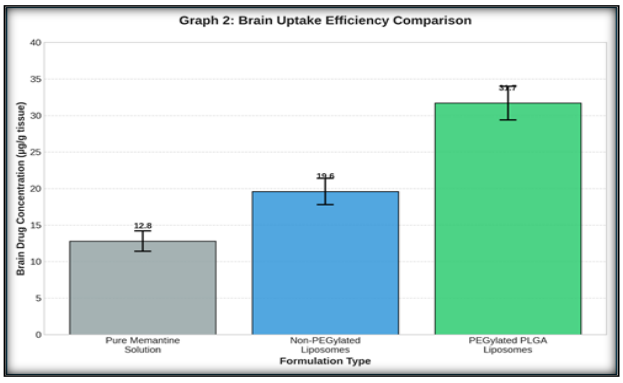


Figure 2: Brain Uptake Efficiency

DISCUSSION

The present study has proven the technique of Quality-by-Design (QbD) for optimizing memantine loaded PEGylated PLGA liposomal nanoparticles for better nose to brain delivery in the context of Alzheimer disease. The optimized formulation possessed good physiochemical parameters, such as low particle size, narrow PDI, high EE and sustained drug release profile, improved nasal permeation and good stability profile. This latest discovery adds to the applications of nanotechnology-enabled intranasal drug delivery systems in the targeting of drugs to the central nervous system.

The optimized formulation showed an effective particle size (PS) of 156.2 ± 3.9 nm while the EE was 89.8 ± 1.9%, showing good formulation uniformity and encapsulated nanoparticle size. Rani and Chawla,[1] showed that memantine-loaded PLGA nanocarriers exhibited desirable nanoscaled dimensions and superior drug loading efficiency to be used for Alzheimer's treatment. Similarly, Pandian et al,[2] pointed to the fact that smaller sized liposomal nanocarriers that more readily penetrate the blood–brain barrier and also enter the neuronal cells have been presented.

The intranasal delivery potential in the present study was in line of previous experiments conducted by Handa et al,[3] who reported that intranasal self-nano-emulsifying drug delivery system containing memantine and donepezil exhibited a remarkable brain targeting potential and therapeutic efficacy in experimental Alzheimer models. Likewise, Kaur et al,[4] stated that the formulation of the memantine loaded PLGA nanoparticles exhibited better pharmacodynamic response and neuroprotective activity than the conventional formulation. Our study has a improved permeation profile that could be explained by the use of olfactory transport pathways, provided by the nanoscale size distribution, and penetration of the mucus by PEG.

Optimized formulation revealed sustained release characteristics (for 24 hours) exhibiting diffusion controlled kinetic. These results are similar with that reported by Anand et al,[5] which were obtained from PLGA nanoparticles showing controlled diffusion of polymer and gradual degradation of the matrix. One important benefit of sustained release in the management of Alzheimer's disease is that it can lower the need for dosing, thus enhancing compliance with the therapy. Taliyan et al,[6] also further emphasized the ability of the nanocarrier mediated sustained release system to increase the therapeutic effect in the brain and decrease their effect on peripheral system.

Formulation stability and permeation efficiency were greatly impacted by PEGylation in the current study. Andrade et al,[7] showed that brain delivery and neuronal uptake are greatly improved when liposomes are

PEGylated and functionalized, which is related to their better mucoadhesion and longer systemic circulation. Similar results were also noted by Cunha et al,[8] who observed both increased drug transport and transport of drugs to Avoid hepatic first-pass metabolism through olfactory pathways with nanoformulations for intranasal administration (IN) modified with PEG. The ex vivo results of the present study demonstrated that the flux and nasal tissue binding of the PEGylated liposomal formulation was found to be very high as compared to the pure memantine solution. Similar observations were reported by Sánchez-López et al,[9] where they showed increased bioaccessibility of memantine from the nanoparticles in the brain and better distribution of memantine-PLGA-peg in the brain in vivo. Additionally, Hassan et al,[10] noted that use of nanoparticles for intranasal delivery of drugs could be one of the most promising ways to overcome these blood–brain barrier limitations in Alzheimer's disease therapy.

Systematic identification and control of critical formulation variables were successfully achieved using the current QbD-based optimization approach to understand the roles they play in determining the performance of the nanoparticles. Similarly, Jadhav and Bele,[11] reported on pharmaceutical optimization approaches for preparation of reproducible and stable memantine-loaded PEGylated PLGA liposomal systems, emphasizing the importance of following the QbD principles to the development of such systems. Earlier optimisation studies of the formulation by Yadav and Sawant,[12] and Ray et al,[13] also proved the critical influence of parameters such as polymer concentration, ratio of surfactant, sonication time and voltage on the synthesis of nanoparticles and its attributes namely particle size, concentration of drug released and percentage of encapsulation efficiency.

The optimized formulation had a stability profile with very small changes in its physicochemical parameters during the storage time, which meant that the formulation was stable in terms of colliquidity. The long term stability results reported here are alike to other PLGA nanoparticle systems fabricated for targeted cancer therapeutics,[14] which helps prove the robustness of the polymeric nanoparticle formulations to be utilized in pharmaceutical applications.

In conclusion, the present study indicates that PEGylated PLGA liposomal systems have potential applications in enhancing the intranasal delivery of memantine using a QbD approach, both in the prospective and retrospective design methodology. Concentrated permeation, sustained release and good stability characteristics all indicate greater possible therapeutic potential in the processing of Alzheimer's disease treatment.

There are some limitations in the present study. The in vivo pharmacokinetic and long-term neurobehavioral evaluation were not extensive, and the investigation was mainly in vitro/ex vivo based. What is more, there is a risk of restricted clinical translation owing to the retrospective optimization design. The optimized formulation's long-term safety, biodistribution, and efficacy in the treatment of Alzheimer's disease patients need to be further evaluated with multicentre preclinical and clinical studies.

CONCLUSION

The present study successfully showed that it is possible to optimize memantine-loaded PEGylated PLGA liposomal nanoparticles in a retrospective manner for better NBD in AD. The optimized formulation showed desirable physicochemical properties, high drug entrapment efficiency, sustained release behavior, improved permeating the nose and stable profile, which suggested its potential for high efficiency in targeting the central nervous system. PEGylation and formulation at the nanoscale played a pivotal role in overcoming the significant challenges that existed with traditional memantine therapies and resulted in improved mucosal penetration and increased duration of drug effect. In conclusion, the results show that the PEGylated PLGA liposomal systems prepared using the QbD concept are promising nanotechnological drug delivery system for enhancing intranasal administration of any type of a therapeutic agent in the treatment of Alzheimer’s disease.

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