Original Article

Development of Carmustine Loaded PLGA-PEG Conjugates for Nose to Brain Targeting

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ABSTRACT

Intranasal drug delivery is a promising route for drug delivery directly to the brain for acute or chronic treatments. A direct route to the brain offers a rapid approach to delivering drugs to the central nervous system without using the parenteral route. Carmustine is a nitrosourea used to treat brain tumors, multiple myeloma, lymphoma, and Hodgkin's disease but its use is limited by a very little half-life in the body fluids. The nanoparticles have shown great potential to overcome problems related to shorten shelf life. The present study aims to develop a nose-to-brain delivery system for Carmustine to prevent degradation and prolong it's bioavailability at the target site. It has shown that the nanoparticles have uniform size and shape and were found to be 231 ± 21.2 nm with 0.128 PDI. The system has stabilized with sufficient surface charge and the zeta potential of the system was found to be -21.2 ± 2.3 mV. After 24 h, cumulative drug release from the prepared system was found to be the maximum release of around 96.69 ± 3.38 in the phosphate buffer pH 6.8.

Keywords: Nose-to-Brain delivery, Nanoparticles, Carmustine, Emulsification Solvent, Evaporation Method.

INTRODUCTION

The World Health Organization (WHO) estimates that 35% of diseases in Europe are brain disorders.[1] Neurodegenerative, cerebrovascular, and cancerous illnesses are the most prevalent neurological c1onditions. However, only 5% of the over 7000 drugs in the comprehensive medicinal chemistry, treat brain diseases, mainly sadness, schizophrenia, persistent agony, and epilepsy.[2-3] Most of these drugs require an improvement in their penetration into the brain. More than 98% of small drugs never reach the brain, which is true for almost all large drugs.[2] This discouraging circumstance is due to the brain's structure, adverse reactions, and the blood-brain barrier's impenetrability (BBB) and blood-cerebrospinal fluid barrier (BCB).

Nanocarriers have emerged as one of the most promising candidates for drug delivery due to their target-specific controlled drug release, biocompatibility, surface modification, and encapsulation of diverse, active molecules, including drugs, peptides, genes, and vaccines.[4] To facilitate the provision of beneficial drugs towards the brain, pharmaceutical manipulation, disruption of the brain barriers, and other methods involving nanocarriers are being utilized. Intranasal drug delivery offers an alternative to the parenteral route for direct delivery to the brain for acute and chronic treatments.[5] Moreover, non-invasive method of administering drugs via intranasal administration with minimal systemic exposure to drugs, results in fewer toxic effects and better patient compliance.[6] Carmustine (CRM), a nitrosourea is used to treat brain tumors, multiple myeloma, lymphoma and Hodgkin's disease.[7-8] Besides, higher volume of distribution, it rapidly metabolizes after intravenous administration with a plasma half-life of 29 min.[9] Therefore, the present study aims to

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develop a nose-to-brain delivery system for Carmustine to prevent degradation and prolong its half-life at the targeted site.

Because of its potential to form NPs, micelles, and microspheres, as well as its biocompatibility, biodegradability, and tolerability, PLGA is a widely studied polymer.[10] PLGA NPs can be required to develop controlled-release dosage forms of small-molecule medicines, peptides, and nucleic acids as drug delivery vehicles.[11] PLGA NPs have been shown to be promising carriers for drug administration across the BBB after suitable copolymerization with PEG and surface modification with linkers. Furthermore, PLGA degrades into non-toxic compounds (H2O and CO2) that are excreted from the body. PLGA is mixed with polyethylene glycol (PEG) to generate PLGA–PEG copolymer NPs to overcome its short half-life.[12-13] Opsonization of the NPs is inhibited by PEGylation. PEG has mostly been used as a major polymer in copolymer synthesis to improve PLGA efficiency, reduce mechanical strength, and increase degradability. The use of these copolymers reduces drug toxicity, improves therapeutic efficacy, and improves drug delivery to the brain across the blood–brain barrier.[14]

MATERIALS AND METHODS

Materials

Carmustine drug was a gift sample from Emcure Pharmaceuticals Ltd. in India, and PLGA and PEG 6000 were procured from Sigma Aldrich. Chemdyes Corporation Rajkot provided all of the chemicals utilized, which were of analytical grade (Gujarat). The Milli-Q® (Millipore, Bangalore, India) water was used throughout the study.

Methods

Drug Excipient Compatibility Studies

An FTIR study was conducted to find out the interaction and compatibility of drug with the excipients. The FTIR spectrum depicts the fingerprint regions representing corresponding functional groups in the compound.[15] The samples of drug and drug with the same proportion of excipients were kept for compatibility study at room temperature for one month. The standard spectrum of drug was then compared with the IR spectrum of samples after one-month study.

Synthesis of PLGA-PEG Conjugates

By coupling PEG diamine with activated PLGA, the PLGA-PEG diblock copolymer was formed by amide linkage method.[16] Dicyclohexylcarbodiimide was used to activate the carboxyl-terminal end of the PLGA using N-hydroxysuccinimide. PEG-6000 diamine was then conjugated to the N-hydroxysuccinimide of the PLGA via amide linkages. The formed PLGA-PEG conjugate was then precipitated and purified by the continuous treatment with cold methanol and ethanol respectively.[17]

Preparation of PLGA-PEG Nanoparticles

The emulsification solvent evaporation method was used to prepare drug-loaded PLGA-PEG nanoformulations (CRM- PLGA-PEG-NPs) (Table 1).[17] The emulsion was formed by the addition of an organic phase containing PEG-PLGA polymer with the drug in acetone to the aqueous phase having 1% Polyvinyl alcohol (PVA) as a surfactant. The o/w emulsion was then sonicated at 50 amplitudes for 60 sec. (Cole- parmer 750-watt Ultrasonic Homogenizer) to reduce the size of the globules in nanometric. The formed nanoparticles were stirred (800 rpm) for 12 hr at ambient temperature to allow for removal of the organic solvent by the process of evaporation. By ultracentrifugation, the nanoparticles were purified at 30,000g for 15 min and washed thrice with deionised water.[18]

Transmission Electron Microscopy (TEM)

TEM was used to determine the nanostructure of CRM-PLGA-PEG nanoparticles (TECNAI-G2, 200 kV, HR-TEM, FEI, Netherlands). A diluted solution of nanoparticles was placed on a sheet of paraffin, then a carbon grid was placed on top of the sample for 1 min, after which it was coated with a drop of phosphor tungstate for 10 sec. and air-dried before TEM examination.[19-20]

Particle size, PDI and Zeta Potential

The particle size and size distribution of the CRM-PLGA-PEG nanoparticles were investigated using a Zeta sizer (Nano ZS 90, Malvern Instruments, UK) at a fixed angle of 90 degrees at 25°C. Before analysis, the nanoparticle dispersion was diluted with millipore water to achieve a measuring speed of 50-200 kilo counts per second (kcps). Zeta potential measurements were performed at 23 V/m electric field strength in an electrophoretic cell. The Helmholtz–Smoluchowski equation was used to compute the zeta potential.[21]

Determination of Encapsulation Efficiency and Loading Capacity of Nanoparticles

A spectrophotometric determination of the amount of unentrapped drug at 280 nm was performed on the supernatant after centrifugation of nanoparticulate dispersion at 20,000 rpm for 30 min to estimate drug entrapment.[22-23] The following equations were used

to calculate the drug encapsulation efficacy (AE) and loading capacity (LC) of nanoparticles:

$$\% \text{ AE} = [(A-B)/A] \times 100$$

$$\% \text{ LC} = [(A-B)/C] \times 100$$

Where A represents the quantity of drug, B represents the quantity of free drug, and C represents the weight of Nano formulations.

Thermal Analysis

TGA was used to determine the thermal stability of the CRM-PLGA-PEG nanoparticles. The samples of drug and nanoparticles were subjected to thermal analysis in TGA (Linseis STA PT 1000, Germany) by heating at a heating rate 15°C/min and a temperature between 30°C-700°C, under nitrogen purge. TGA thermograms were obtained by correlating the differences in an initial and final weight reduction of samples of drug and drug in nanoparticles respectively.[23-24]

FTIR Analysis

The synthesis of PLGA-PEG conjugates and the encapsulation of drug in the system were confirmed using FTIR spectroscopy. It provides vital information about drug-polymer interactions and the fate of drug in the body. FTIR was used to study the FTIR spectra of Carmustine and CRM-PLGA-PEG nanoparticles (Shimadzu, India).

In vitro Release Study

A dialysis bag diffusion method was used to estimate how much drug is released from CRM-PLGA-PEG nanoparticles (Yang *et al*. 2019). A dialysis bag (Sigma Aldrich molecular weight cut of 12 kDa) was filled with a 2 ml suspension of CRM-PLGA-PEG nanoparticles equivalent to 5 mg of carmustine, tied at both ends, and suspended in 50 ml of phosphate buffer saline (pH-7.4). The antioxidant ascorbic acid (200 µg/mL) was added.[24] Throughout the method, the nanoparticle was agitated at 50 rpm, and the temperature was kept at 37±0.5°C. 0.5 mL of samples were extracted and reconstituted with the same volume of phosphate buffer saline at different time intervals (pH-7.4). Spectrophotometric measurements of drugs were performed at 280 nm using a Shimadzu UV-1601 (Japan).

Stability Studies

An evaluation of the stability of the formulation and the effect of environmental factors over time may be carried out, which determines the product's shelf life.[25] It ensures the preparations stays within its predefined limits for a prescribed length of time. Moreover, it provides a detailed understanding of physicochemical changes that leads to formation of toxic degradants which in turns reduces efficacy and increased toxicity. Therefore, the stability studies of CRM-PLGA-PEG nanoparticles were carried out after storing them at specific temperature and humidity conditions as per ICH stability guidelines for three months.[26] In turns, particle size, polydispersity index, and residual drug concentration were evaluated for stability of nanoparticles.[27]

RESULT AND DISCUSSION

Transmission Electron Microscopy (TEM)

The surface morphology of CRM-PLGA-PEG nanoparticles were investigates using TEM and depicted in Figure 1. It confirms the spherical shape and homogeneity of formed nanoparticles. Although the particles were smooth and showed no signs of rupture, they were highly consistent. hey were all separate, with no signs of aggregation.

Particle Size and PDI Measurement

The stability of the nanoparticles and their effect through the body is significantly affected by the particle size of the system. The particle size of the optimized CRM-PLGA-PEG nanoparticles were estimated using zeta sizer and found to be 231±21.2 nm which was also confirmed by TEM image (Figure 3). Moreover, the less polydispersity index values i.e. 0.128 confirms the homogeneity of the nanoparticles.

Zeta Potential

The Zeta potential of the nanoparticulate system was found to be -21.2±2.3 mv (Figure 2), a negative surface charge on the particles is because of the presence of negative functional groups of the PLGA-

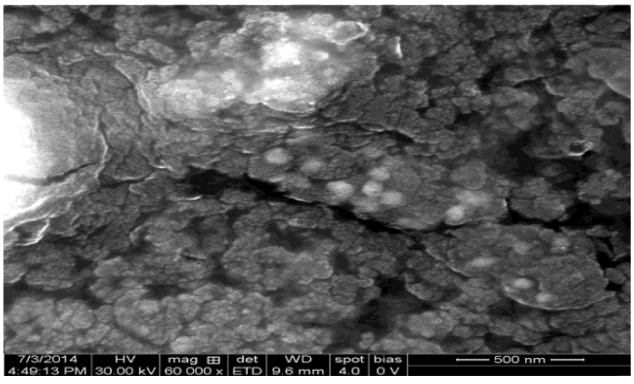

Figure 1: TEM photomicrograph of optimized CRM-PLGA-PEG nanoparticles.

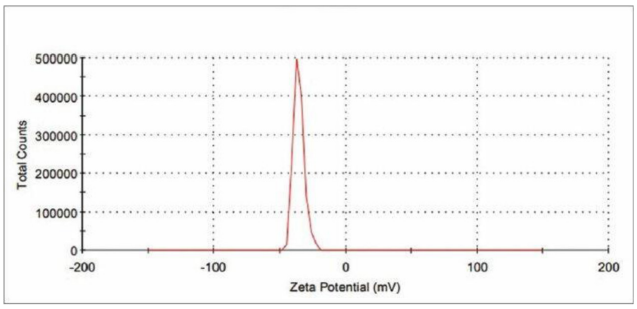

Figure 2: Zeta Potential of Carmustine.

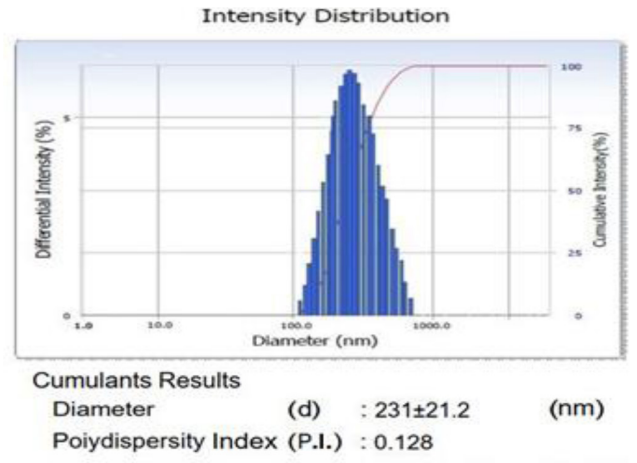

Figure 3: Particle size Zetasizer report.

PEG conjugate. The high zeta potential prevents agglomeration by generating repulsive forces which stabilize the nanoparticulate system.[28]

Entrapment efficiency, Loading capacity

In formulation development, entrapment efficiency and loading capacity are important parameters. The CRM-PLGA-PEG nanoparticles has of 46.74±3.2% and 54.6±2.7% entrapment efficiency and loading capacity, respectively.

FTIR Analysis

The FTIR spectrum (Figure 4) of drug and CRM-PEG-PLGA nanoparticles were evaluated for the major functional groups and to confirm the encapsulation of the drug in the nanoparticulate system. The FTIR spectrum of nanoparticles shows the peak of amide linkage which is characteristic peak of PLGA-PEG conjugation (Table 2). Also, the peaks of major functional groups of pure drug was altered significantly indicating encapsulation of the drug in the nanoparticulate system.

Thermal Analysis

The study into the thermal behaviour of plain drug and optimized CRM-PLGA-PEG nanoparticles was studied and depicted in Figure 5. The percent weight reduction in samples heated to 600°C were recorded and compared with initial weight. Figure 4 illustrates the weight reduction effects of plain drug and CRM-PLGA-PEG nanoparticulate system. From the thermogram it was observed that the rate of percent weight reduction of plain drug was higher as compared to the drug in nanoparticles which might be due to the encapsulation of drug into the nanoparticles.

In- vitro Release Study

The amount of drug release from PLGA-PEG nanoparticles was estimated using the dialysis bag diffusion technique. After 24 hr, cumulative drug release from PEGylated NPs formulations showed a maximum release of about 96.69±4.6 % in the phosphate buffer pH 6.8. Figure 6 shows the cumulative % drug release from nanoparticles and plain drug. The drug release was found to be slower and prolonged in the nanoparticulate system as compared to plain drug which was released completely within 12 hr. The significant difference in drug release was the evident for the improvement of

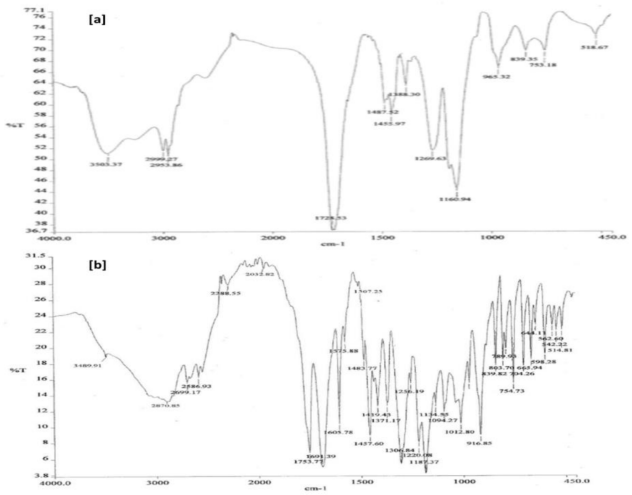

Figure 4: FTIR spectrum of (a) Carmustin (b) Physical mixture of Chitosan-carmustine nanoparticles.

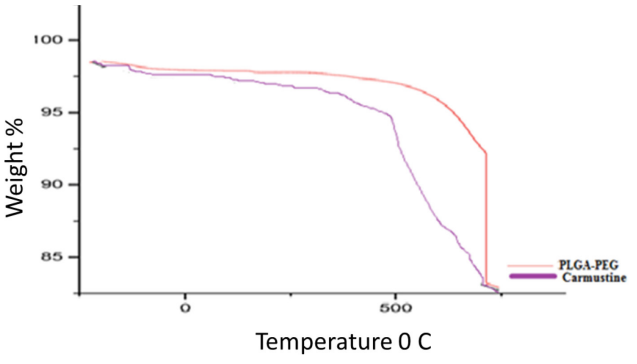

Figure 5: Thermal Analysis of Nanoparticles.

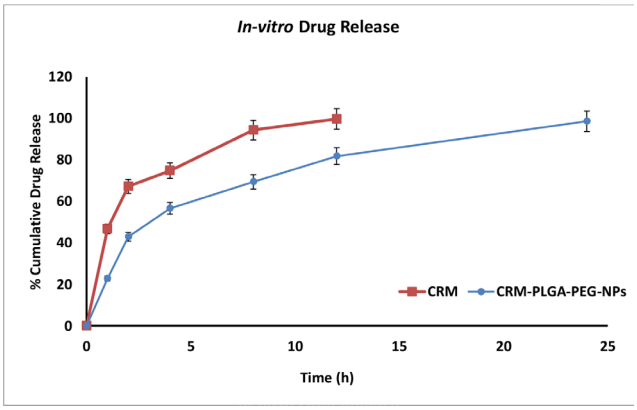

Figure 6: *In-vitro* percent cumulative drug release.

Table 1: Formulation table of Nanoparticle.

Sl. No	Material	F-1	F-2	F-3
1	Polymer Concentration (PEG-PLGA) (mg/ml)	5	10	15
2	Drug Concentration (CARMUSTINE) (mg/ml)	0.5	1	2
3	Ratio of solvent to Water	0.1	0.3	0.5

Table 2: Wave number of functional groups of Carmustine.

Sl. No.	Wave number	Carmustine Functional group
1	1100-1200 cm^{-1}	C=H
2	1200-1300 cm^{-1}	COO- (carboxylic acids)
3	1300-1400 cm^{-1}	C-N
4	1400-1450 cm^{-1}	COO- (carboxylic acid)
5	1500-1600 cm^{-1}	-
6	1600-1650 cm^{-1}	-
7	1750-1730 cm^{-1}	C=O

therapeutic concentration of drug for prolong time and therefore can increase the bioavailability of drug at target site.

Stability Studies

The stability of drug-loaded CRM-PLGA-PEG nanoparticles was assessed for three months at refrigerated storage (5 ± 2°C) and accelerated storage (25 ± 2°C) storage as per ICH guidelines. After three months of storage at 25± 2°C and 5± 2°C temperatures, CRM-PLGA-PEG nanoparticles showed no significant change in particles size, PDI, and entrapment efficiency. This might be due to the PLGA-PEG conjugates is said to be very versatile and stable polymer which ensures the stability of encapsulated drug from various environmental changes.

CONCLUSION

The effect of formulation variables on the performance of Carmustine-loaded PLGA-PEG conjugates for Nose to Brain Targeting was studied in this work. FTIR analysis confirmed that the PLGA-PEG diblock copolymer was synthesized via an amide linkage. PLGA is mixed with polyethylene glycol (PEG) to synthesize PLGA–PEG copolymer NPs to overcome its short half-life. The use of these copolymers reduces drug toxicity, improves therapeutic efficacy, and improves drug delivery to the brain across the blood–brain barrier. The nanoparticles have the desired properties like particle size, zeta potential, and drug release characteristics. The pharmacokinetic properties of the drug such as C_{max}, half-life, and AUC have also been improved as a result of controlled-release targeted drug delivery. As a result, the present drug delivery systems have the dual benefit of extending controlled drug release while also increasing drug bioavailability at the target site. Furthermore, positive results from stability studies indicate that the present innovative delivery method has long-term storage potential. Direct brain targeting may provide a rapid way to deliver Carmustine from the nose to the brain. The findings showed that the drug delivery mechanism used in this investigation could be an effective non-invasive method for increasing Carmustine access to the brain.

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CONFLICT OF INTEREST

The authors declare no Conflict of interest.

ABBREVIATIONS

PLGA: poly (lactic-co-glycolic acid); **PEG:** polyethylene glycol; **nm:** nanometer; **PDI:** polydispersity index; **mv:** millivolt; **hr:** hour; **°C:** degree centigrade; **WHO:** world health organization; **BBB:** Blood brain barrier; **BCB:** Blood cerebrospinal fluid barrier; **CRM:** Carmustine; **min:** minute; **FTIR:** Fourier Transform Infrared Spectroscopy; **NPs:** nanoparticles; **o/w:** oil in water; **sec:** second; **UK:** united kingdom; **V/m:** volt per meter; **rpm:** revolution per minute; **AE:** encapsulation efficacy; **LC:** loading capacity; **TGA:** thermogravimetry; **ml:** milliliter; **mg:** milligram; **TEM:** Transmission electron microscopy; **cm:** centimeter.

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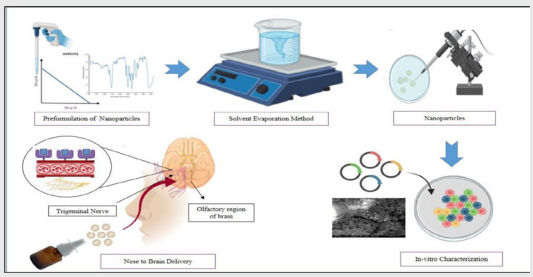
SUMMARY

Due to their target-specific controlled drug delivery, biocompatibility, surface functionalization, and encapsulation of different, active molecules like as drugs, peptides, genes, and vaccines, nanocarriers have emerged as one of the most promising possibilities for drug delivery. Furthermore, non-invasive drug administration by intranasal administration with less systemic exposure to pharmaceuticals, resulting in fewer adverse effects and improved patient compliance. To design a nose-to-brain Carmustine delivery system that will avoid degradation and extend the half-life of the drug at the target site. Drug-capsulated PLGA-PEG nanoformulations were prepared using the solvent evaporation method, and the formulated nanoparticles were evaluated using TEM, particle size, PDI and zeta potential, encapsulation efficiency and loading capacity, FTIR, *in-vitro* release study, and stability studies. The developed nanoformulations had the requisite size, zeta potential, and drug release characteristics, as well as the ability to be stored for long periods of time.

PICTORIAL ABSTRACT



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