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RESEARCH PAPER

Enhancing the Performance of Lipophilic Chemotherapeutic Agent via Polymeric Nanoparticle Fabrication

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ABSTRACT

Lomustine, a chemotherapeutic agent used in the treatment of brain tumors and other malignancies, is limited by its poor water solubility and systemic side effects. This study aimed to formulate and evaluate lomustine-loaded nanoparticles to enhance its solubility, stability, and controlled release profile. Nanoparticles were prepared using the nanoprecipitation method with polylactic-co-glycolic acid (PLGA) as the polymeric carrier. The formulations were evaluated for particle size, zeta potential, drug loading, entrapment efficiency, and in vitro drug release. The optimized formulation exhibited a particle size of 198.1 nm, zeta potential of -17.2 mV, and an entrapment efficiency of 74.16%. FTIR and DSC analyses confirmed the absence of drug-polymer interactions. The in vitro release study demonstrated a sustained release profile over 24 hours, suggesting the potential of the nanoparticle formulation to improve therapeutic efficacy and reduce side effects. These findings support the application of PLGA-based nanoparticles as a promising delivery system for lomustine in cancer therapy.

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INTRODUCTION

Nanoparticles (NP) are nano-sized (10-500 nm) particles which are usually spherical. They could be composed from polymer, oil, lipid, protein and others. Due to their shape and size, nanoparticles have wide range of applications and benefits including deliver and targeting medications since they can target cancerous cells and avoiding the healthy cells. This can lead side effect lowering and enhancing the drugs' efficacy. In addition, nanotechnology-based drug delivery systems have significant effect on enhancing the stability, solubility, permeability and then bioavailability of medications [1-3].

Nanoparticles could be constructed to specifically target tissues or cells like malignant

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as the medications only deliver and release when reached the required site. The unique nano-sized particles added these advantages to this delivery system. Furthermore, the nanoparticles can bypass the available biological barriers such as BBB (blood brain barrier) [4-6].

There are many types of nanoparticles including nanoemulsion, solid lipid nanopartic;es, nanostructured lipid carrier, liposomes, nanoemulsion, niosomes, ethosomes, polymeric nanoparticles and others. Polymeric nanoparticles are solid, colloidal particles with sizes ranging from 10 nm to 1 µm. Polymeric nanoparticles can have the shape of a nanosphere or a nanocapsule, depending on how they are produced. In nanospheres, the drug is equally distributed throughout a matrix system, whereas in nanocapsules, the drug is contained within a hollow that is encased in a polymeric membrane. Both synthetic and natural polymers—such as proteins and carbohydrates—are typically hydrophilic. Both prepolymerized and process-polymerized synthetic polymers are utilized in synthesis. Because polymeric nanoparticles may deliver medications in a variety of organ systems, they offer enormous promise as drug carriers [7, 8]. The polymeric nanoparticles have many strengths involving enhancing the carried drug solubility, improving the drug in-vivo retention and eventually the overall drug bioavailability [9, 10].

Lomustine is an alkylating chemotherapy that used for Hodgkin's disease, brain tumors and other types of cancers. It is a nonselective for the malignant cells and can affect the normal cells as well. Therefore, it causes a serious side effect of myelosuppression. These side effect could only reduce by lowering the drug dose and this leading to reduce its cytotoxicity and the therapeutic effects as well as increasing the drug targeting to the cancer tissue. Lomustine undergoes extensive hepatic metabolism due to its lipophilicity and hence its half-life is short of 94 min [11,12]. Therefore, incorporation of the drug into nanocarrier could enhancing drug solubility and bioavailability as well as improving the selectivity and targeting to the cancer cells.

The aim of the study is to formulate lomustine as nanoparticle to improve its solubility and reducing its first pass metabolism and finally enhancing the target tissue selectivity by using different polymers.

MATERIALS AND METHODS

Materials

Lomustine was purchased from Hyperchem, China. Ethyle cellulose (EC) was bout from Keshi, China. Poly vinyl pyrrolidone (PVP) and acetone were from Merck, Germany. Poly ethylene glycol (PEG) and Tween 20 were from Himedia Laboratories, India. Dimethyl Sulphoxide (DMSO) was bought from Alpha Chemika, India.

Preparation of lomustine nanoparticles

Lomustine loaded polymeric NP were formulated by nanoprecipitation technique. Nine different formulas as shown in Table 1. For organic soluble polymer (EC), first, lomustine and EC were weighing and dissolved in acetone and then in DMSO to prepared the organic phase. Tween 20 was dissolved in distilled water. Then, the organic phase was added drop by drop to aqueous phase with stirring (at 500 rpm). The endpoint was the precipitate appearance and it was separated and dried. For water soluble polymer (PVP) and PEG,

Table 1. Lomustine NP formulas.

Formulas	Amount of drug (mg)	Amount of polymer (mg)	Amount of DMSO (ml)	Amount of acetone (ml)	Amount of D.W (ml)
F1	40	40 of EC	2	5	5
F2	40	40 0f PVP	2	5	5
F3	40	40 of PEG	2	5	5
F4	40	20 of EC	2	5	5
F5	40	20 of PVP	2	5	5
F6	40	20 of PEG	2	5	5
F7	20	40 of EC	2	5	5
F8	20	40 of PVP	2	5	5
F9	20	40 of PEG	2	5	5

the organic phase was prepared by dissolving the drug in DMSO and then acetone. The aqueous phase was prepared by dissolving PVP, PEG and Tween 20 in distilled water. Then, the rest was done as mentioned before with the organic polymers [12, 13].

Characterization of lomustine NP

NP size, polydispersity index (PDI) and zeta potential

Lomustine NP' average particle size and size distribution were assessed using dynamic light scattering (DLS) with Nanotrac (Microtrac, Germany). Zeta potential is a crucial metric for assessing a colloidal/dispersion system's stability. The Zeta potential of every formulation is determined using the same instrument for size determination. The measurements were performed in triplicate and the mean was taken [14].

Entrapment efficiency

This test was performed by determining the lomustine amount in the supernatant (w) after centrifugating each formula using spectrophotometric method at the drug lambda max. Then, this amount was subtracted from the total lomustine amount the should be presented when prepared (W). The entrapment efficiency then calculated as follow [15]:

$$\%\ \text{dRUG Entrapment} = \left(\frac{W - w}{W}\right) \times 100$$

In vitro release study of lomustine from NP formulations

The release of lomustine from NP formulas was assessed using a dissolution apparatus type II. One milliliter of each formula was added to vessels filled with acidic buffer solution (900ml) using dialysis bag. At predetermined intervals (5 min, 15 min, 30 min, 45 min, 1 hr, 1.5 hr, 2 hr, 2.5 hr, 3 hr, 3.5 hr, and 4 hr), samples of 5 ml were withdrawn from the medium solution and then replaced it with fresh buffer. The samples were analyzed using UV spectrophotometer [16, 17].

Scan electron microscopy (SEM) of the optimum formula

The SEM was used to examine the optimum formula to determine and confirm its shape and size. This test was made to determine the shape, size and distribution of the particles within the optimal formula [18].

Statistical Analysis

One way ANOVA was used in order to determine the significance different between the findings.

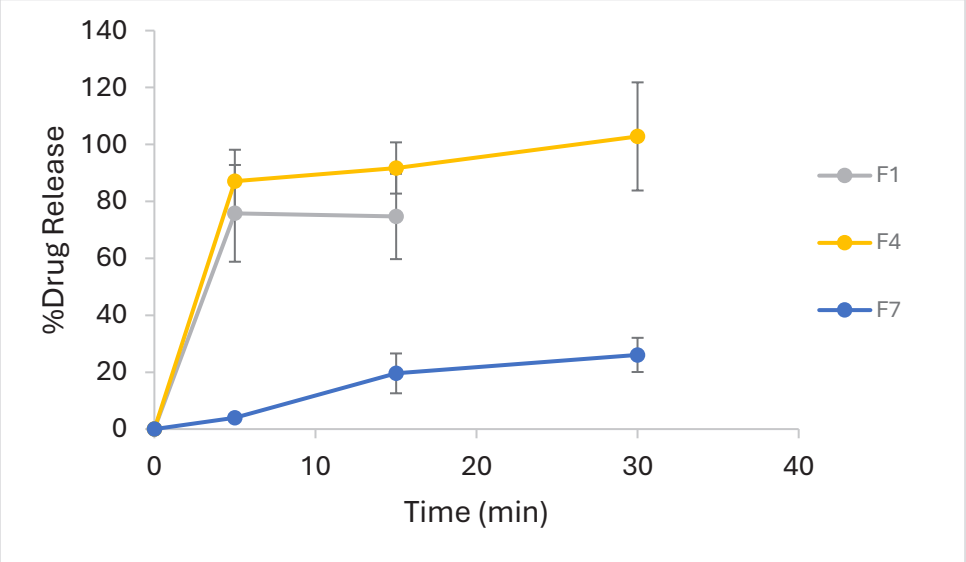

Fig. 1. The in vitro release study of the formulated lomustine nanoparticles using acidic buffer (900ml) and dissolution apparatus type II and dialysis bag 8,000-12,000 Da.

RESULTS AND DISCUSSION

Evaluation test of NP formulas

Particle size, PDI and zeta potential

The particle size, PDI and zeta potential results of the formulated nanoparticles were shown in Table 2. Because smaller nanoparticles have a bigger surface area and a faster release rate in the aqueous media, size and size distribution are important factors in determining the drug delivery of nanoparticles. They also affect absorption, bioavailability, and dissolution. A particle size analyzer (Nanotrac, Germany) was used to measure the particle size and polydispersity index (PDI) of each produced formulation. The average particle size varied from 23 to 93 nm. F7 had the smallest particle size, measuring around 21 nm, out of all the formulas with the lowest standard deviation [17].

Lower values of the PDI indicate more homogeneous and monodisperse nanoparticles. The PDI represents the size distribution of the nanoparticles. As seen in Table 2, the PDI values ranged from 0.19 to 0.53 based on the formulation factors. With a PDI value of 0.18, F4 exhibited the lowest value, indicating that the nanoparticles were stable and homogenous. Formulation F4 with a particle size of 63 nm and PDI of 0.18, was determined to be the best ones based on the data. Using the permeability study and TEM, F4 was further assessed [18,19].

Zeta potential, which reveals electrical characteristics at the medium-fluid layer interface surrounding dispersed particles, is one of the important elements describing stability. It serves as an indicator of the attraction or repulsion that formed between the particles.

Zeta potential of previously made methotrexate nanoparticles was measured using a zetasizer; the findings are displayed below Table 2. The optained zeta potential for the formulated lomustine nanoparticles ranged from 10 to 28 mV. Notably, a higher zeta potential correlates with a decrease in particle aggregation because of electrostatic repulsion, which enhances the stability of nanoparticles. In particular, the chosen Formula F4's zeta potential yielded a value of 28 mV with low standard deviation values. Zeta potential results suggest that the surface of these nanoparticles was positively charged. However, it's crucial to remember that because attractive Vander Waals forces are at work, low zeta potential might lead to particle aggregation and flocculation. In addition, zeta potential values only offer partial information about the stability of nanoparticles because the total physical stability of the resulting nano suspensions depends on a number of other factors, including the properties of the material, the presence of suspension [20-22].

Entrapment efficiency

The ratio of the experimentally determined percentage of drug content to the actual or theoretical mass of drug used to prepare the nanoparticles is known as entrapment efficiency, The manner and polymer-drug combination are what determine the loading efficiency. Higher amounts of hydrophobic pharmaceuticals are encapsulated by hydrophobic polymers, whereas bigger amounts of hydrophilic medications are entrapped by hydrophilic polymers [23,24]. The degree of drug loading will depend on a number of formulation characteristics, including the kind of emulsifier, the weight ratio of polymer to drug, and the ratio of organic to aqueous phase. Drug entrapment efficiency as a function of polymer are shown in Table 2. The ranges of the data were 73%–92%. PVP and PEG nanoparticles had poor entrapment efficiencies but EC nanoparticles had excellent efficiencies. Less entrapment efficiency may be caused by the hydrophobic nature of

Table 2. The particle size, PDI, zeta potential and Entrapment efficiency of the formulated nanoparticles.

Formula Code	Particle size (nm)±SD	PDI	Zeta potential (mV)	Entrapment efficiency
F1	68.6±1.02	0.44	10.1	86.32±2.02
F2	89.4±0.97	0.37	16.9	74.54±2.99
F3	52.5±0.76	0.53	15.8	77.33±3.1
F4	63±0.55	0.18	28	85.69±3.3
F5	129.6±2.8	0.2	22.1	72.94±4.55
F6	23.01±1.66	0.28	14.2	72.88±1.91
F7	81.36±2.7	0.37	18.0	92.22±2.66
F8	38.6±3.01	0.19	10.1	76.39±6.11
F9	92.6±2.2	0.27	16.9	79.28±4.34

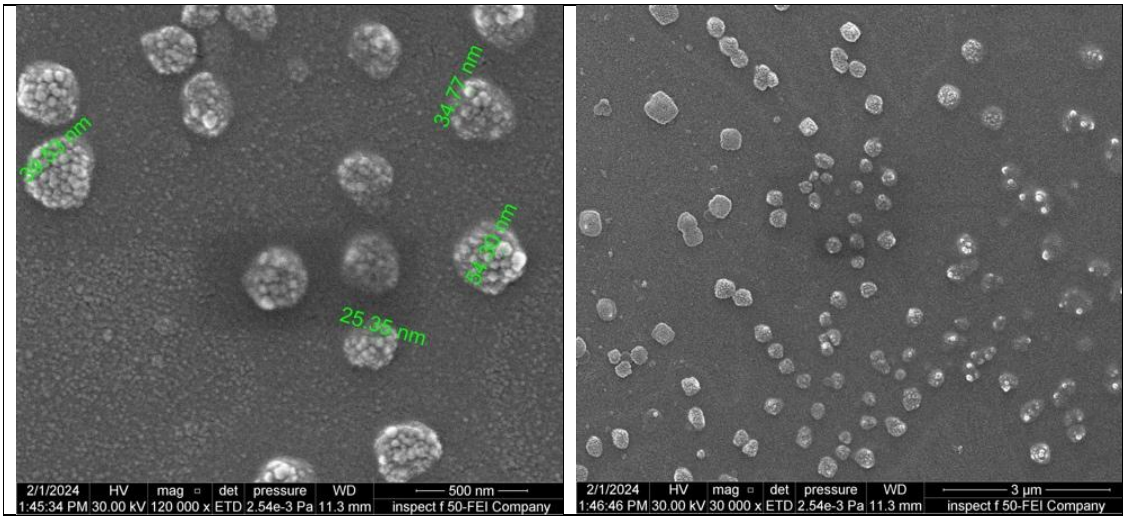

Fig. 2. SEM result of the optimized nanoparticle formula of lomustine (F4).

lomustine, however entrapment efficiency may be enhanced by raising the amount of hydrophobic polymer, ensuring that there will be enough polymer available to entrap the drug present in the solution [25, 26].

In vitro release study of lomustine from NP formulations

Only the three higher formulations with higher entrapment efficiency and passed the other test in vitro were subjected to release study including the formulations with EC as formulating hydrophobic polymer, as shown in Fig. 1. Formula F4 had the high and faster release and this might be due to the smaller particle size that leading to faster drug dissolution and release [27-31].

SEM of the optimum formula

Scanning Electron Microscopy, or SEM, is a type of electron microscopy that uses high-energy electrons to continuously scan a sample's surface for surface characteristics. This technique provides a thorough visual analysis of the nanostructure of materials including thin films and powders. Furthermore, signals generated by the sample aid in the acquisition of data on the size, shape, and surface morphology of methotrexate polymeric nanoparticles, as well as their physical and structural characteristics. SEM analysis was performed to describe the size, shape, and surface morphology of the particles and to create a three-dimensional diagram for the optimal formulation of lomustine nanoparticles (F4). Thus, the SEM pictures for the optimum formula revealed homogeneities and a sample with high dispersion and spherical shaped (as shown in Fig. 2). These findings from the SEM measurements support the effective synthesis of lomustine nanoparticles with evenly dispersed nano-sized particles [32-33].

CONCLUSION

This study's main goal was to improve lomustine solubility by encapsulating it in polymeric anoparticles. The formulation F4 was selected, and it demonstrated desirable values of particle size, polydispersity index (PDI) and a zeta potential, which indicate homogeneity and stability, respectively. Comparing the lomustine nanoparticles formulations regarding the drug release shown a significant improvement in drug release and permeability according to the particle size. The nano-droplet size was influenced by the EC polymer, increased surface area, and higher release rates. Scanning electron microscopy (SEM) further confirmed the particles' extensive dispersion.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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