OPTIMIZATION OF OLMESARTANPOLYMERIC NANOPARTICLES: A STUDY ON FORMULATION PARAMETERS AND PARTICLE SIZE OPTIMIZATION

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Abstract

This study focuses on the formulation and optimization of Olmesartan polymeric nanoparticles (PNs) to improve the bioavailability and stability of the antihypertensive drug. Polymeric nanoparticles offer advantages such as enhanced drug stability, improved absorption, and sustained release. The study employs techniques like nanoprecipitation and emulsion solvent evaporation for the synthesis of PLGA polymeric nanoparticles. The formulation parameters, including polymer type, concentration, surfactant selection, and processing conditions, are systematically varied and evaluated using statistical designs. The particle size and zeta potential of the nanoparticles are analyzed, and the optimized formulation, OPN5, is selected based on meeting the acceptance criteria for particle size and zeta potential. Stability studies are conducted on OPN5, and its performance is evaluated after storing for three months at 4°C. The results show slight changes in particle size, zeta potential, polydispersity index, drug encapsulation efficiency, and yield, indicating acceptable stability. The development and optimization of Olmesartan PNs have the potential to enhance the therapeutic efficacy of the drug by addressing its limitations in bioavailability and stability.

Keywords: Olmesartan, Polymeric nanoparticles, Optimization, Bioavailability, Stability, Particle size, Zeta potential.

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INTRODUCTION

Olmesartan is a widely used antihypertensive drug belonging to the class of angiotensin II receptor antagonists. It exerts its therapeutic effects by blocking the binding of angiotensin II to its receptors, thereby promoting vasodilation and reducing blood pressure. Despite its clinical efficacy, Olmesartan has limited bioavailability and stability, which can hinder its therapeutic effectiveness [1].

Polymeric nanoparticles have gained significant attention in recent years as a promising drug delivery system. These nanoparticles can enhance the pharmacokinetic properties of drugs, such as bioavailability, stability, and targeted delivery. The development of Olmesartan-loaded polymeric nanoparticles offers a potential solution toovercome the limitations associated with conventional formulations of the drug [2].

The encapsulation of Olmesartan within polymeric nanoparticles offers several advantages. Firstly, the nanoparticles can protect the drug from degradation, thereby enhancing its stability. Secondly, the small size of the nanoparticles allows for improved drug penetration and absorption at the target site. Furthermore, the sustained release of Olmesartan from the nanoparticles can provide a prolonged therapeutic effect, reducing the frequency of drug administration [3].

Various techniques can be employed for the fabrication of Olmesartan polymeric nanoparticles, including nanoprecipitation, emulsion solvent evaporation, and nanoprecipitation-assisted high-pressure homogenization. Each technique has its advantages and limitations, and the selection of the most suitable method depends on the desired particle size, drug loading efficiency, and scalability [4, 5].

The optimization process will involve systematic experimentation to identify the optimal formulation parameters. Factors such as polymer type, concentration, surfactant selection, and processing conditions will be evaluated to determine their impact on the physicochemical properties and drug release characteristics of the nanoparticles [3-6].

The development and optimization of Olmesartan polymeric nanoparticles hold great potential for improving the therapeutic outcomes of this antihypertensive drug. The enhanced bioavailability, stability, and sustained release properties offered by the nanoparticles can contribute to better patient compliance and treatment efficacy in the management of hypertension.

This study aims to optimize the formulation and preparation of Olmesartan polymeric nanoparticles to improve its therapeutic efficacy. The optimization process involves the selection of appropriate polymers, particle size, and drug-polymer ratios to achieve desirable physico-chemical properties and sustained drug release.

Preparation of Olmesartan Polymeric Nanoparticles (PNs)

The single emulsification solvent evaporation and Nano precipitation method were used to synthesize PLGA polymeric nanoparticles (200nm). Typically, known amounts of PLGA polymer and Olmesartan were mixed to ethyl-acetate, which was thoroughly agitated to ensure that all ingredients were completely dissolved in the solvent. The organic phase solution was then slowly added into the agitated aqueous PVA solution along with poloxamer. This mixture was homogenised at 5000 RPM in a high-speed homogenizer, then sonicated for 5 minutes in a continuous mode with a probe sonicator (Q sonica Probe Sonicator).A magnetic stirrer (Remi, India) was used to gently swirl the produced oil in water (O/W) emulsion at room temperature until the organic solvent evaporated. The nanoparticles were recovered by centrifugation at 20,000 rpm for 15 minutes and then washed twice or three times with water in order to remove the surplus surfactant. The purified nanoparticles were lyophilized with 5% manitol to produce a fine powder of nanoparticles that was deposited in vacuum desiccators and maintained there [7-9].

Experimental design for formulation of PNs

For the optimization study, 2^3 statistical designs with three levels, two factors, and eight runs were used, which were carried out with the help of design expert software (State easy Inc, Minneapolis USA, design Expert 11). The independent variables polymer concentration (A in mg), surfactant concentration (B in ml), and homogenization rate (C in min) were chosen and set at a high or low level based on the variable's result. 8 OPNs formulations are developed and characterised according to this design for particle size (Y1) and Zetapotential (Y2), which are dependent variables and were chosen as response parameters. These designs reveal the independent variable's main effect on the dependent variable. Table 1 depicts its optimization approach [10-13].

Stability Studies

From the above calculated results, only the optimized Olmesartan PNs was subjected to stability studies. PNs were filled in capsules and stored in 4°C±2°C. After 3 months these capsules were analysed at a specified period of time and measured to determine the polydispersity index (PI), particle size (nm), zeta potential (mV). Each formulation was checked for their reproducibility of results while manufacturing [14-16]

RESULTS AND DISCUSSION

The mean particle sizes for all the formulations are presented in Table 1 and Figures 1. In general, the particle sizes for all the Olmesartan PNs formulations was found to be in the range of 193.59 ± 46.8 to 434.4± 24.4nm, based on the effect of independent variable in the process of formulation. But the acceptance criteria, the PS of polymeric nanoparticle should be 60-200nm. As per the acceptance criteria, the formulation OPN5 (5mg A factor; 1.0 ml of B factor and 20 min of C factor) shows 193.59 ± 46.8nm. The formulation OPN6 (5mg A factor; 0.5 ml of B factor and 10 min of C factor) shows 197.6 ± 24.6nm. Remaining formulation OPN1 to OPN4, OPN7 and OPN8 formulations particle size was found to be more than desired range i.e. >200nm. From the results it was inferred that on decrease in polymer with increase in surfactant concentration there is a decrease in particle size. Further increase in particle size it leads to more increase in particle size.

The zeta potential for all the formulations is presented in Table 1 and Figure 1. In general, the zeta potential for all Olmesartan PNs was found to be in the range of -10.2 ± 1.64mV to-35.6 ± 1.24mV, primarily based on the effect of surfactant in the process of formulation. But the acceptance criteria of ZP of polymeric nanoparticle should be found between ±30 to ±60 mV. As per the acceptance criteria, the formulation OPN5 (5mg A factor; 1.0 ml of B factor and 20 min of C factor) shows maximum ZP of -35.6 ± 1.24mV. Remaining formulation was found to be less than desired range i.e. <-30mV. From the data it was inferred that there is increase in surfactant and homogenization rate there is an increase in zeta potential.

To further discuss the relationship between the formulation parameters and particle size of Olmesartan polymeric nanoparticles (OPNs), we can analyze the response surface graphs. These graphs provide visual representations of how the independent variables (polymer concentration, surfactant concentration, and homogenization rate) affect the dependent variable (particle size).

Based on the provided information, the particle sizes of OPNs ranged from 193.59 ± 46.8 to 434.4 ± 24.4 nm. The acceptance criteria for polymeric nanoparticles is typically set to be between 60-200 nm, indicating the need to optimize the formulation to achieve desired particle sizes.

The response surface graph for particle size can illustrate the impact of polymer concentration, surfactant concentration, and homogenization rate on the particle size of OPNs. By analyzing the graph, we can observe the trends and relationships between these variables.

From the results, it is inferred that a decrease in polymer concentration coupled with an increase in surfactant concentration leads to a decrease in particle size. This trend suggests that lower polymer concentrations allow for the formation of smaller nanoparticles, while higher surfactant concentrations contribute to better dispersion and stabilization of the particles.

However, it is important to note that beyond a certain point, further increases in surfactant concentration may lead to an increase in particle size. This observation indicates that there might be an optimal surfactant concentration that achieves the desired particle size.

The homogenization rate also influences the particle size, as seen in the response surface graph. It appears that an increase in homogenization rate can contribute to a decrease in particle size. This effect can be attributed to the enhanced dispersion and reduction in particle aggregation achieved through increased homogenization.

Overall, based on the response surface graph and the provided data, the optimized formulation OPN5 (5mg A factor, 1.0 ml of B factor, and 20 min of C factor) meets the acceptance criteria for particle size. The formulation OPN6 (5mg A factor, 0.5 ml of B factor, and 10 min of C factor) also falls within the desired range. However, further optimization may be required for the remaining formulations (OPN1 to OPN4, OPN7, and OPN8) to achieve the target particle size range.

By utilizing response surface methodology and analyzing the relationship between formulation parameters and particle size, it is possible to optimize the formulation of Olmesartan polymeric nanoparticles to meet the desired specifications for enhanced bioavailability and stability.

The comparative stability study data for OPN 5 before and after conducting stability studies was shown in Figure 2, 3. The PS nm, ZP mV, PI, %EE and % Yield of OPN 5 during preparation was found to be 193.59 ± 46.8nm, -35.6 ± 1.24mV, 0.469 ± 0.10, 95.42 ± 2.68, 97.92 ± 2.42

and OPN 5 after performing stability studies i.e. after 3 months on storing in 4˚± 2˚ C was found to be 196.42 ± 34.12nm, -34.2 ± 1.42, 0.478 ± 0.12, 94.38 ± 2.78, 96.42 ± 3.56.

Table No 1: Optimization of Olmesartan Polymeric Nanoparticle and evaluation of effect of independent variables on dependent variables by 2^3 factorial design

Run	Independent variables			Dependant variables	
	Factor A: Polymer Concentration [Level code/mg]	**Factor B: Surfactant Concentration [Level code/ ml]**	**Factor C: Homogenization rate [Level code/min.]**	**PS* Y1 nm**	**ZP * Y2 mV**
OPN 1	-1 / 5	1 / 1.0	-1 / 10	356.4 ± 26.4	-10.24 ± 1.24
OPN 2	1 / 10	-1 / 1.0	-1 / 10	284.8 ± 32.0	-14.6 ± 1.48
OPN 3	1 / 10	-1 / 0.5	1 / 20	434.4 ± 24.4	-10.2 ± 1.64
OPN 4	1 / 10	1 / 1.0	1 / 20	312.6 ± 32.8	-18.8 ± 2.02
OPN 5	-1 / 5	1 / 1.0	1 / 20	193.6 ± 46.8	-35.6 ± 1.24
OPN 6	-1 / 5	-1 / 0.5	-1 / 10	197.6 ± 24.6	-21.3 ± 1.26
OPN 7	1 / 10	1 / 1.0	-1 / 10	338.2 ± 34.4	-15.4 ± 1.46
OPN 8	-1 / 5	-1 / 0.5	1 / 20	254.6 ± 36.8	-16.6 ± 1.68

Acceptance criteria: Particle Size (PS) = 60-200nm; Percentage entrapment efficiency (%EE) = >85%

Figure 1. Particle Characteristics; (A) PS, PI; (B) ZP of (OPN5) of Optimized Polymeric Nanoparticle (OPN5)

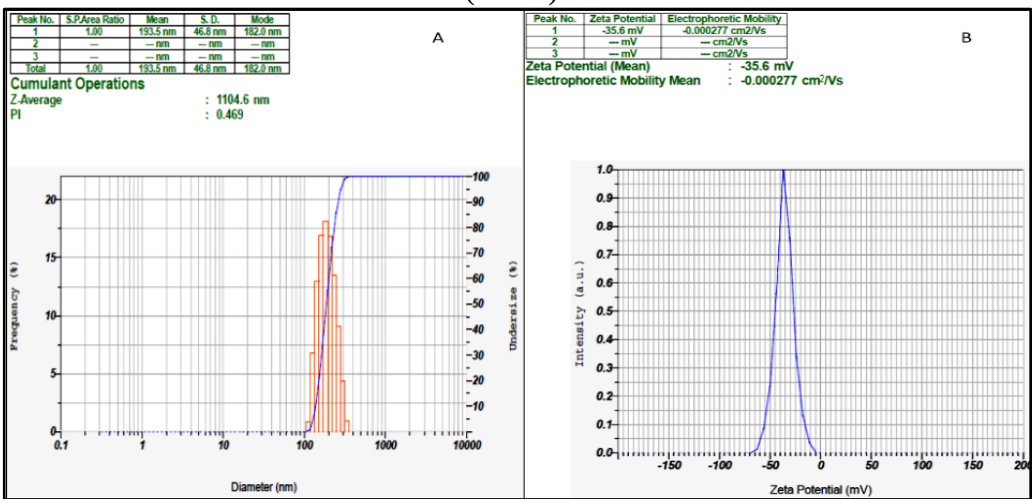


Figure 2.(A) PS, PI and (B) ZP report for Optimized Polymeric Nanoparticle (OPN 5) at 4˚± 2˚ C after 3 months

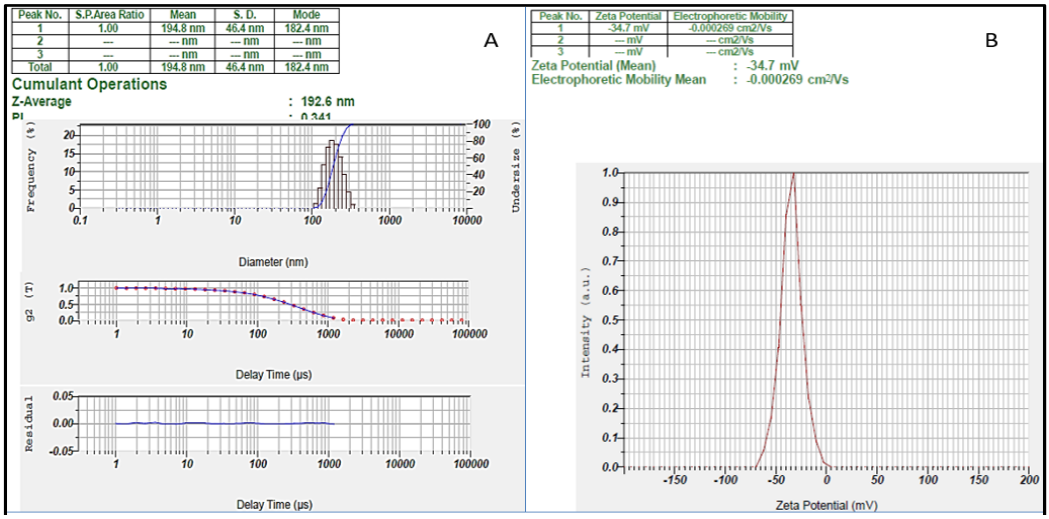
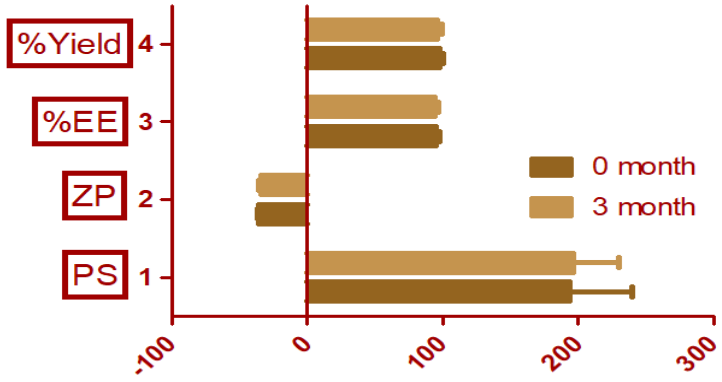


Figure 3. Comparative stability study data for OPN5 before and after conducting stability studies



CONCLUSION

Based on the results obtained, it can be concluded that formulation OPN5 (5mg A factor; 1.0 ml of B factor and 20 min of C factor) met the acceptance criteria for particle size and zeta potential. This formulation exhibited a particle size of 193.59 ± 46.8 nm and a zeta potential of -35.6 ± 1.24 mV. However, further optimization may be necessary to improve the particle size of other formulations within the desired range. The data also suggested that increasing the surfactant concentration and homogenization rate led to an increase in zeta potential. The stability study of OPN5 showed acceptable changes in particle size, zeta potential, polydispersity index, drug encapsulation efficiency, and yield after 3 months of storage. Further investigations and optimization are recommended to enhance the stability and performance of Olmesartan polymeric nanoparticle formulations.

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