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Optimizing the Formula of Polymeric-Based Aripiprazole Nanosuspension Using Response Surface Methodology for Intranasal Drug Delivery

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ABSTRACT

This study aimed to optimize the formula of aripiprazole nanosuspension for intranasal drug delivery. Response Surface Methodology (RSM) was employed to determine the influence of independent variables, including drug concentration, polymer concentration, and the ratio of polymer combination, on the nanosuspension characteristics. The parameters under investigation were particle size (d mean), polydispersity index, and drug content. Fifteen formulas generated from Box-Behnken Design (BBD) were prepared using the combination of high-shear homogenization–ultrasonication method, and the Design Expert software was applied for optimum formula determination. The result showed significant effects of the independent variables on the nanosuspension characteristics, with particle sizes ranging from 143.6 – 334.6 nm, PDI values of 0.302 – 0.649, and drug content of 98.7 – 102.1%. The predicted optimum formula had a drug concentration of 28 mg/mL in the organic solvent, polymer concentration of 1.5% (w/v), and HPMC to PVP ratio of 1.4 with desirability of 0.94. Additionally, it exhibited desirable characteristics, such as a particle size of 171.2 ± 11.4 nm, a PDI value of 0.317 ± 0.02, and a high drug content of 100.04 ± 0.65%. The optimized formula was also evaluated for its morphology using TEM, *in vitro* duration of mucoadhesion and physical-chemical stability study. In conclusion, the aripiprazole nanosuspension prepared and optimized using RSM exhibited favorable characteristics, including small particle size, narrow distribution, and high drug content.

Keywords: Aripiprazole, High Shear Homogenization, Nanosuspension, Ultrasonication

INTRODUCTION

Aripiprazole is a second-generation atypical antipsychotic drug used for the treatment of schizophrenia, primarily acting on the central nervous system (CNS) by selectively binding to the dopamine D_2 and serotonin (5-HT2c) receptors (Sawant *et al*., 2016). However, its oral administration faces limitations due to the exhibition of lower solubility in water (Brittain, 2013), leading to hindered dissolution and varying absorption in the gastrointestinal tract. Being a substrate of the P-glycoprotein (P-gp) efflux pump at the blood-brain barrier (BBB), aripiprazole experiences restricted availability in brain tissue (Kirschbaum *et al*., 2010; Wang *et al*., 2009). Consequently, an alternative route is needed to ensure enhanced availability and therapeutic effect.

Intranasal drug delivery represents a promising alternative to increase the bioavailability of aripiprazole in the CNS by enabling direct delivery and bypassing the BBB (Mallick *et al*., 2020). Numerous studies have explored the potential of this route, specifically for treating CNS diseases, including neurodegenerative or psychiatric conditions (Gänger & Schindowski, 2018). The drug can reach the brain through the olfactory and trigeminal nerves in the nasal membrane, which have diameters of 100 – 700 nm (Morrison & Costanzo, 1992). Therefore, particles internalized through these nerves are expected to

be smaller than the mentioned diameters. Delivery through the intranasal route encounters challenges, such as the mucociliary cleansing effect, which shortens the residence time of drugs in the nasal mucosa, necessitating the use of appropriate dosage forms (Costa *et al*., 2021).

Nanosuspension, an aqueous dispersion of insoluble drugs with particle sizes below 1000 nm, offers a potential solution to enhance drug dissolution rate and stability (Elmowafy *et al*., 2021). This nanoparticle dispersion is stabilized using polymers, surfactants, and inorganic particles (Sole, 2013). To achieve nanosuspensions with optimal characteristics and prevent aggregation during storage, it is crucial to optimize influential formulation parameters, such as the ratios and concentrations of polymers and surfactants. Several critical parameters must be controlled, including particle size, size distribution, and drug content, which are influenced by the type and concentration of stabilizing polymers and the active substance (drug). Consequently, optimization is essential to obtain the most suitable nanosuspension formula.

Response Surface Methodology (RSM) is a valuable tool for formulation optimization as it facilitates investigating the interactions between multiple factors that impact the tested response. Additionally, RSM enables the creation of mathematical models, reduces the number of tests required for optimization, and saves time and resources (Aydar, 2018).

Examining the relationship between variables is necessary to obtain a stable and robust nanosuspension formula. In this study, the aripiprazole nanosuspension was optimized as a treatment candidate for intranasal delivery to the brain using RSM with the Box-Behnken Design (BBD). The effect of independent variables, including aripiprazole concentration in organic solvents and the concentration and ratio of HPMC to PVP (a combination of stabilizing polymers with mucoadhesive properties), was evaluated on particle size, PDI, and drug content.

MATERIALS AND METHODS

Chemicals and Reagents

Aripiprazole was purchased from Jinlan Pharm (Hangzhou, China), the aripiprazole reference standard was purchased from Europe Pharmacopoeia, Hydroxypropyl methylcellulose (HPMC) grade K100LV was purchased from Dow Chemical (USA), PVP-K30 was purchased from Zhejiang Chemicals (Hangzhou, China). All chemical reagents and HPLC mobile phase were purchased from Merck (Germany), and double distilled water was purchased from Ikapharmindo (Indonesia).

Experimental Design

To statistically evaluate the main effects of key factors on the characteristics of the nanosuspension, a three-factor, three-level BBD was employed. These included the drug concentration in the organic phase (mg/mL) (X1), polymer concentration as a stabilizer (%) (X2), and the HPMC to PVP ratio (X3). The responses examined were the produced particle size (Y1), PDI (Y2), and drug content (Y3). Both of the coded and actual values of these factors in the BBD (Table I). A total of 15 experimental runs were performed, involving three center points, to minimize errors.

Table I. Box-Behnken Design for Optimization of Aripiprazole Nanosuspension.

Independent Variables	**Level**		
	-1	**0**	**+1**
Drug concentration in the organic phase (X1)	20	40	60
Polymer concentration (X2)	0.5	1	1.5
HPMC to PVP ratio (X3)	0.5	1	2
Dependent Variable	**Constraints**		
Particle size (Y1)	Minimize		
PDI (Y2)	Minimize		
Drug Content (Y3)	Maximize		

Preparation of Aripiprazole Nanosuspension

Aripiprazole nanosuspension was prepared using a high-shear homogenization-ultrasonication technique. Initially, aripiprazole was dissolved in tetrahydrofuran as the solvent phase. Simultaneously, the antisolvent phase was created by dispersing different ratios of HPMC and PVP in phosphate buffer (pH 5.8). The resulting product was cooled to 4°C, and 2.5 mL of the solvent phase was rapidly introduced into 50 mL of the antisolvent while homogenizing with a High Shear Homogenizer (Ultraturax) at 10,000 rpm for 5 minutes. The mixture was ultrasonicated using a probe sonicator (Qsonica) with a power input of 50% for 5 min. The organic solvent was then evaporated under reduced pressure using a rotary evaporator (Buchi).

Characterization of Nanosuspension

Particle Size and PDI

The particle size and PDI of the nanosuspension were determined using a particle size analyzer (Malvern Zetasizer ZS90) in triplicate. A drop of the formulation was appropriately diluted in 10 mL of deionized water.

Drug Content

The drug content was analyzed through the RP-HPLC method as described by Kumbhar *et al*. (2020) with slight modifications. Chromatographic separation was achieved using a mobile phase composed of methanol and acetonitrile (80:20 v/v) at a flow rate of 1.0 mL/min, while a C-18 column (4.6 mm x 250 mm, 5 µm) served as the stationary phase. This process was conducted at room temperature (25°C) with the UV detector set at a wavelength of 254 nm. For sample preparation, 50 µL of the nanosuspension was diluted using the mobile phase to a final volume of 10 mL and filtered with a 0.45 µm PTFE syringe filter. Subsequently, 20 µL of the solution was injected into the HPLC system for analysis. A calibration curve of the standard solution was prepared by diluting the working stock solution with the mobile phase to obtain respective concentrations of aripiprazole ranging from 0.5 to 20 ppm. The following equation was applied in calculating the drug content:

$$\text{Drug content (\%)} = \frac{\text{Observed drug content}}{\text{Theoretical drug content}} \text{ X } 100$$

Morphology

The morphology of nanosuspension particles was observed using a transmission electron microscope (TEM) (JEOL-JEM 1400) at an accelerating voltage of 100 kV. The sample was prepared by placing a drop of nanosuspension on a copper grid and stained with a phosphotungstic acid solution. The sample was allowed to dry and examined.

***In Vitro* Duration of Mucoadhesion**

Duration of mucoadhesion was assessed by applying 1 g of nanosuspension containing 0.1% red colorant on the goat nasal mucosal surface, which was attached over a plate fixed at an angle 40°C relative to the horizontal plane. Phosphate buffer saline (PBS) pH 7.4, warmed to 37°C, was pumped over the tissue at a 5 mL/min rate. The duration for complete washing of the formulation was detected based on the presence of colour (Khan *et al.,* 2010).

Stability Study

The stability study was performed for the optimized formula by storing the nanosuspension at high (40±2°C), room (30±2°C), and low (5±3°C) temperatures for four weeks. The particle size, PDI, and drug content were appropriately evaluated.

RESULTS AND DISCUSSION

Nanosuspension Development and Preparation Method

Aripiprazole nanosuspension for nose-to-brain drug delivery was developed using a combination of high-shear homogenization (HSH) and ultrasonication methods. The HSH process employed high-speed mixing elements as the rotor and a static part as the stator, generating substantially higher shear compared to traditional stirring devices. This instrument facilitated high shear mixing, leading to a reduction in nanosuspension particle size through shear stress, turbulence, and cavitation forces (Ubgade *et al*., 2021). The speed of homogenization is a critical factor influencing the final particle size, with faster homogenization yielding smaller particles (Patel *et al*., 2021).

Tetrahydrofuran was used as the organic solvent to dissolve the hydrophobic drug. The soluble drug in the organic solvent was mixed with the antisolvent-containing stabilizer using HSH to induce precipitation, leading to the formation of amorphous nanoparticles. Generally, the amorphous state of the drug was unstable and exhibited higher solubility than the crystalline state, making the particles prone to growth through the Ostwald ripening mechanism (Lindfors *et al*., 2006; Xia *et al*., 2010). To control the growth of particles formed, the preparation method was combined with ultrasonication. Moreover, sonication could prevent agglomeration, slow down the growth rate, and produce uniformly sized, spherical amorphous particles (Sinha *et al.,* 2013). Stabilization of the nanosuspension was achieved using a combination of two polymers, HPMC and PVP. The methoxy and hydroxypropyl groups of HPMC interact with the hydrophobic surface of the drug to allow adsorption on the particle surface and facilitate stabilization by modulating steric interactions that prevent particle collision (Abdelbary *et al*., 2013). Meanwhile, PVP, a polymer with carbonyl, cyano, and methylene groups, is widely used as a stabilizer for nanosuspensions.

Table II. Observed response for aripiprazole nanosuspension formulations (mean ± SD) with input variables of drug concentration in the organic phase (X1), polymer concentration (X2), and HPMC to PVP ratio (X3)

Input Variables				Output Parameters		
F	**X1**	**X2**	**X3**	**Particle Size (Dv_{mean}) (nm)**	**PDI**	**Drug Content (%)**
F1	60	1	2	165.3 ± 20.2	0.649 ± 0.01	102.0 ± 0.17
F2	40	1.5	2	143.6 ± 11.4	0.444 ± 0.15	101.8 ± 0.82
F3	20	1	2	210.2 ± 21.3	0.389 ± 0.01	98.7 ± 0.27
F4	60	0.5	1	240.9 ± 23.1	0.381 ± 0.02	102.1 ± 0.73
F5	40	1	1	201.8 ± 29.7	0.398 ± 0.13	100.5 ± 0.35
F6	40	0.5	0.5	208.2 ± 23.3	0.381 ± 0.04	101.9 ± 0.58
F7	20	1	0.5	212.7 ± 23.8	0.550 ± 0.03	99.8 ± 0.43
F8	40	1	1	217.5 ± 30.3	0.395 ± 0.10	100.4 ± 1.72
F9	40	1	1	201.5 ± 24.1	0.388 ± 0.13	100.1 ± 1.21
F10	40	1.5	0.5	252.8 ± 26.2	0.308 ± 0.02	100.0 ± 0.67
F11	60	1	0.5	334.6 ± 43.2	0.335 ± 0.05	101.2 ± 0.92
F12	40	0.5	2	194.7 ± 23.7	0.426 ± 0.11	100.5 ± 0.40
F13	60	1.5	1	245.1 ± 16.7	0.302 ± 0.03	101.6 ± 0.52
F14	20	1.5	1	169.4 ± 67.1	0.364 ± 0.03	99.2 ± 0.17
F15	20	0.5	1	197.7 ± 50.0	0.386 ± 0.01	100.3 ± 0.54

This molecule contains a significant hydrophobic group and a strong hydrophilic pyrrolidone moiety. With the hydrophobic carbon chain component, PVP inhibits nanosuspension aggregation by repelling particles, creating a steric hindrance effect. (Koczkur *et al*., 2015). Ahmed *et al*. (2018) The combination of HPMC and PVP has been reported to control particle growth, yielding smaller particle size distribution and higher drug loading compared to using a single polymer (Ahmed *et al*., 2018). Both polymers possess mucoadhesive properties, enhancing the residence time of the nanosuspension when applied to the nasal mucosa.

Optimization of Nanosuspension by BBD

The nanosuspension formula was optimized through the BBD, generating 15 runs with three center points per block, using the Design Expert software. The independent variables included drug concentration in the solvent phase (X1), polymer concentration (X2), and HPMC to PVP ratio (X3), while particle size (Y1), PDI (Y2), and drug content (Y3) were set as dependent variables. The responses observed from the runs, indicating that the particle size, PDI, and drug content ranged from 143.6 – 334.6 nm, 0.302 – 0.649, and 98.7 – 102.1 %, respectively (Table II). A quadratic model was employed for each response. The R^2, SD, and coefficient of variation values for each response can be found in the supplementary data

Three-dimensional graph illustrating the interaction between the independent and dependent variables. The correlation plot between the experimental and predicted values of the response can be found in the supplementary data.

Effect of Independent Variables on Particle Size

The observed mean diameter (d mean) of the nanosuspension particles varied from 143.6 nm to 334.6 nm. The polynomial equation analysis demonstrated the significance of the model ($p < 0.05$), with an F-value of 19.37 and a quadratic sequential p-value of 0.0023. An F-value of 2.46 indicated an insignificant lack of fit, suggesting that this model could navigate the design space with adequate precision (18.879), providing a good signal. The polynomial equation describing the particle size (Y1) was as follows:

$$Y1 = +192.47 + 17.62A - 7.50B - 36.82C + 8.12AB - 41.18AC - 21.98BC + 18.63A^2 - 12.29B^2 + 19.62C^2$$

An increase in drug concentration (indicated by the positive coefficient of A) led to an elevation in particle size. This result aligned with a previous study on the formulation of resveratrol nanosuspension (Hao *et al.,* 2014). Higher drug concentrations in the solvent phase might cause significant supersaturation and a faster nucleation rate, accelerating particle agglomeration through collision, thereby producing larger particles (Kakran *et al*., 2012).

An increase in polymer concentration (negative coefficient of B) and a higher HPMC to PVP ratio (negative coefficient of C) decreased the particle size of the nanosuspension. Stabilizer polymers are vital in formulating nanosuspension, as they are responsible for maintaining physical stability. Their role involves wetting the surface of the hydrophobic drug particles thoroughly, as well as providing a steric hindrance that can prevent agglomeration and Ostwald's ripening of nanosuspension. The overly high surface energy of the particles initiated by the reduction of large particles to smaller sizes can be decreased with a sufficient amount of stabilizer (Hao *et al*., 2014).

Higher concentrations of the polymer could adhere to the particle surface more quickly and form a mechanical barrier against crystallization by preventing drug molecule incorporation into the crystal lattice, ultimately leading to smaller particles (Kassem *et al*., 2017). This result aligned with a previous study that developed clotrimazole nanosuspension (Gajera *et al*., 2019).

Effect of Independent Variables on PDI

PDI values of the developed formulations ranged from 0.302 to 0.649, with all formulas exhibiting low PDI except for F1 (0.649). Its values lower than 0.5 corresponded to a narrow size distribution of particles, indicating uniform distribution in the formulation (Anggraini *et al*., 2021). The model for PDI was found to be significant ($P < 0.0001$) with an F-value of 141.93. The lack of fit F-value of 4.83 was determined to be statistically insignificant. The adequate precision value of 47.04 indicated a sufficient signal. The polynomial equation for PDI was as follows:

$$Y2 = +0.402 + 0.017A - 0.016B + 0.042C - 0.14AB + 0.117AC + 0.023BC + 0.028A^2 - 0.063B^2 + 0.05C^2$$

The positive coefficients of A and C suggested that a greater PDI value would be obtained with an elevation in both drug concentration within the solvent and the HPMC to PVP ratio. Conversely, the negative coefficient B indicated that PDI decreased with increasing polymer concentration.

Higher drug concentration in the solvent phase could lead to particle agglomeration during precipitation. At higher concentrations, multiple nuclei tended to form at the interface between solvent and anti-solvent phases during mixing, initiating aggregation and the development of larger and inhomogeneous particle size distribution (Kakran *et al*., 2012). Moreover, higher drug concentration led to increased solution viscosity, hindering the diffusion of the solvent and antisolvent phases. This could cause a non-uniform supersaturation and non-uniformity of drug particles formed (Zhang *et al*., 2009).

In contrast, higher polymer concentration decreased the PDI value. This might be due to the need for an adequate polymer concentration to help stabilize the formed particles by creating a steric barrier that hinders Ostwald ripening and subsequent agglomeration (Ubgade *et al*., 2021). Both HPMC and PVP, as polymeric molecules, adsorbed to the droplet surface, preventing contact between adjacent particles through steric hindrance and promoting particle stability. This event prevented further growth and generated a uniform particle size distribution (Kassem *et al*., 2017; Kocbek *et al*., 2006).

The third parameter studied that affected the nanosuspension characteristics was the combination of HPMC and PVP with different ratios. Furthermore, an increase in the HPMC to PVP ratio was believed to yield smaller particle sizes but elevate the PDI values. According to reports, PVP solutions have substantially lower viscosities than HPMC solutions (Dalvi & Dave, 2009). Therefore, raising the HPMC to PVP ratio may enhance the viscosity of the system, reducing the mobility of the nuclei/particles and the frequency of collisions, as well as generating smaller particles (Sinha *et al*., 2013). The higher viscosity of the solution can prevent diffusion between the solvent and anti-solvent during precipitation and the transmission of ultrasonic vibration during sonication, leading to inhomogeneous particle size and a higher PDI of the nanosuspension (Lindfors *et al*., 2006; Xia *et al*., 2010).

Effect of Independent Variables on Drug Content

The drug content of all formulations was close to 100%, with the lowest value being 98.7% in F3 and the highest being 102.1% in F4. The F-value of 182.82 indicated that the model was significant (p-value < 0.0001). The lack of fit F-value of 4.52 suggested that it was not statistically significant. The adequate precision of 42.89 indicated a sufficient signal. The polynomial equation for drug content (Y3) was as follows:

$$Y3 = +100.48 + 1.17A - 0.143B - 0.0012C + 0.1400AB + 0.4863AC + 0.7859BC - 0.1616A^2 + 0.4609B^2 + 0.1140C^2$$

Based on the equation, it can be concluded that the drug content increased with the increase in

Table III. Process parameters for optimum formula and predicted and observed values of the nanosuspension characteristics.

Factors	**Optimized Level**		
Drug Concentration (mg/mL)		28	
Polymer Concentration (%b/v)		1.5	
HPMC to PVP Ratio		1.4	
Desirability		0.94	
Responses	**Predicted**	**Observed**	**Residual***
Particle size (nm)	159.3	171.2 ± 11.4	-11.9
PDI	0.33	0.317 ± 0.02	0.01
Drug content	100	100.04 ± 0.65	-0.04

* Residual = Predicted – Observed

drug concentration in the organic solvent (positive value of A). Conversely, an elevation in the HPMC to PVP ratio and polymer concentration (indicated by the respective negative value of coefficients B and C) led to a decrease in drug content.

The Selection of Optimized Formula for Aripiprazole Nanosuspension

The desirability function from numerical optimization techniques was used to determine the optimized formula for aripiprazole. Furthermore, the constraints on particle size, PDI, and drug content were applied to the software, and the formula with the highest desirability was selected as the optimized choice. The actual results matched the predicted PDI and drug content values, with a slightly higher particle size and a residual value of 11.9 (Table III). The t-test result showed no significant difference between the actual and predicted values ($P>0.05$), supporting the validity of the regression model.

Optimization of the function to the response yielded the optimum formula presented in Table 4. An actual experiment run was performed to validate the optimal results. The obtained optimum formula exhibited a small particle size (171.2 nm) with homogeneous distribution (PDI of 0.317) and a high drug content reaching 100.04%. This actual result was matched with the predicted response of the Design Expert software.

Moreover, the measured high drug content demonstrated that the nanosuspension was well dispersed. Small and homogeneous particles in nanosuspension often provide lower sedimentation properties than conventional suspensions, making drugs to be more evenly dispersed over a long time and highly stable. Nanosuspensions share similar properties with solutions compared to suspensions (Eerdenbrugh *et al*., 2009).

The optimized aripiprazole nanosuspension formula could be considered a suitable candidate for intranasal drug delivery due to its small particle size and high drug content. Besides, most drugs are known to be transported from the nasal mucosa to the brain through internalization in the olfactory nerve with a diameter of less than 700 nm (Morrison & Costanzo, 1992). A particle size below 300 nm has been reported to be optimal for efficient drug delivery to the brain through the nasal route (Patel *et al.,* 2021). A drug content reaching 100% in nanosuspensions indicates effective dispersion without any large particles settling at the bottom, ensuring even distribution (Ubgade *et al*., 2021)

Particle Morphology

The particle morphology was observed using transmission electron microscopy (TEM) (Figure 2). The TEM image showed that nanosuspension has a particle in a uniform spherical shape, and no aggregation was observed. The particle size was found to be below 200 nm, which is considered small, and the size was distributed evenly.

***In Vitro* Duration of Mucoadhesion**

The duration of mucoadhesion for the optimized ARP nanosuspension was 111±10.58 s. The formula was found to easily flow through the membrane, which can be retained for less than 5 min. This might be due to the use of low viscosity – low molecular weight of polymer (grade LV).

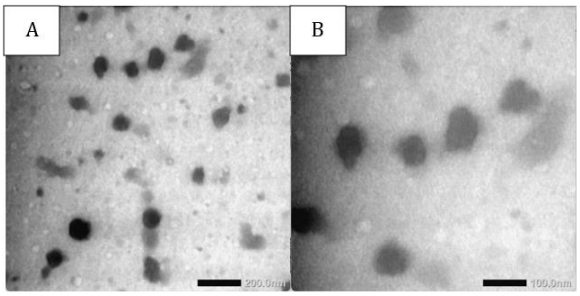

Figure 1. Morphology of optimized ARP nanosuspension observed using TEM imaging at (A) 20.000x and (B) 40.000x magnification

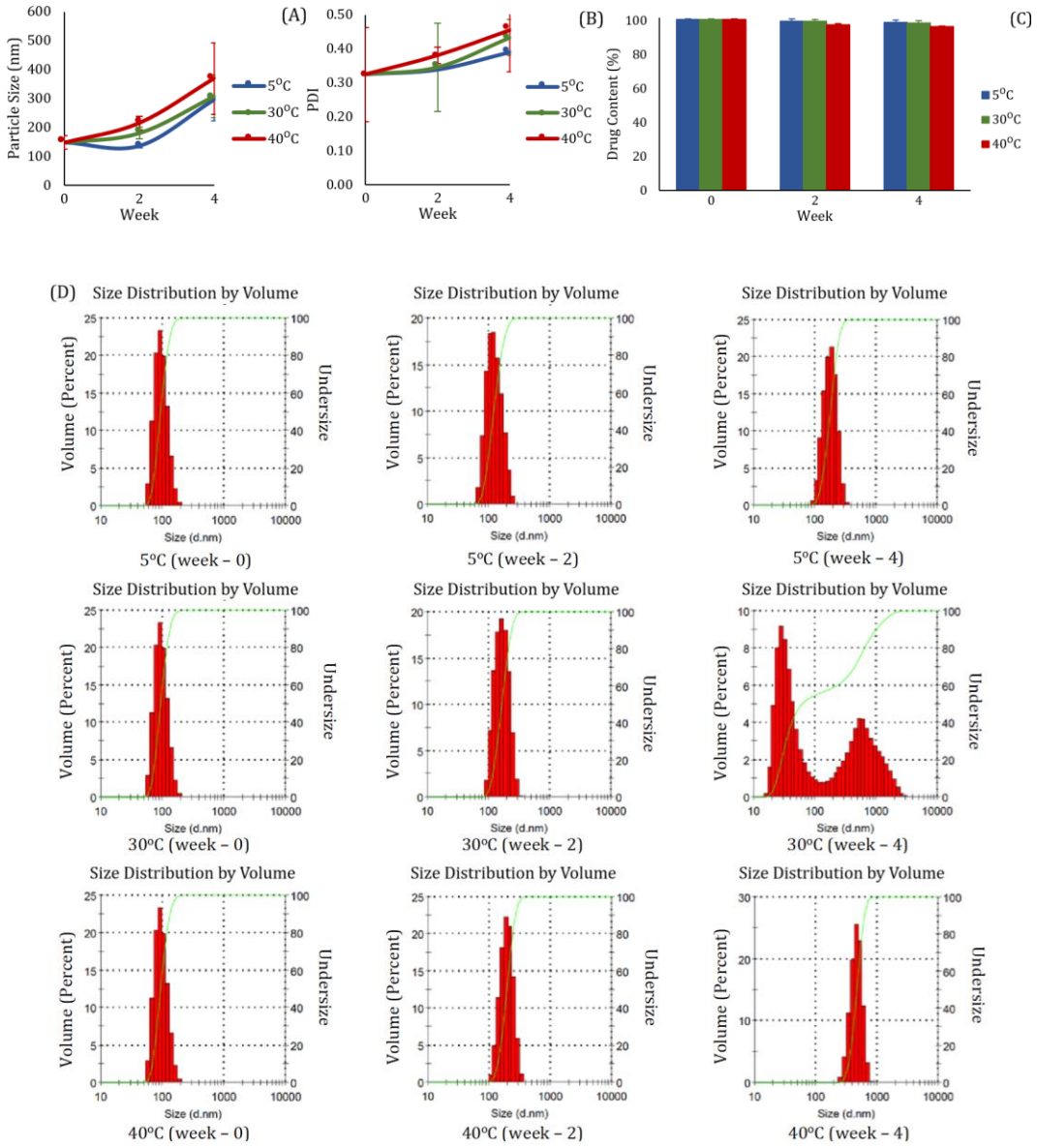

Figure 3. (A) Particle size (nm), (B) PDI, (C) Drug Content (%), and (D) Particle Size Distribution of ARP Nanosuspension at different storage temperatures over 30 days.

The mucoadhesive force usually increases with the molecular weight and concentration of the polymer, namely HPMC and PVP, due to more hydroxyl groups being available for hydrogen bond formation (Khan *et al.,* 2010). In this study, the stabilizers used were both non-ionic polymers. Another strategy to increase the duration of mucoadhesion of nanosuspension can be using an additional ionic polymer or surfactant to give a charge to the particle. Based on the literature, the positively charged molecule can interact with the negative site on the nasal membrane, leading to stronger adhesion and longer retention time in the mucosa (Khan *et al.,* 2010).

Stability Study

The physical and chemical stability of aripiprazole nanosuspension was investigated at three different conditions over 30 days by measuring the particle size, PDI, and drug content (Figure 3). The particle size was found to be increased over time in all storage conditions. However, the size was still within the nano range below 400 nm. The lowest increase occurred at a storage temperature of 5°C followed by 30°C and 40°C with a final particle size of 295.4 ± 72.5 nm, 307.80 ± 73.3 nm, and 368.90 ± 123.4 nm, indicating that the nanosuspension was better stored at low temperatures. The particles were also still distributed homogeneously, indicated by the PDI value at week four being <0.5.

Based on the particle size distribution graph, particle degradation occurs after being stored for four weeks in three different conditions, characterized by changes in size distribution where particles with larger sizes were formed (Figure 3D). Particles with a larger size were caused by the formation of aggregates during storage. Nanosuspension is a thermodynamically unstable colloid dispersion system. Therefore, aggregation is an inherited property of nanosuspension due to the tendency of the nanosized system to reduce the Gibbs free energy (Wang *et al.,* 2013). The increase in particle size and PDI can also occur due to the Ostwald ripening mechanism in which larger particles grow at the expense of the smaller particles, which usually happens in nanosuspension with high free energy (Verma *et al.,* 2011). Coarse particles grow at the expense of the redissolution of smaller particles because smaller particles are more soluble than larger ones, so mass transfer occurs from fine to coarse particles (Wang *et al.,* 2013). Additional electrostatic stabilization using ionic polymer or surfactant might be needed to create a more stable system through a combination of steric-electrostatic stabilization. Another approach for further improving the physical stability is by solidification process through freeze or spray drying.

The drug content was measured using the HPLC method to determine the chemical stability. The results showed that the drug content of aripiprazole in nanosuspension stored at 5°C and 30°C were stable, with concentrations at week four being 99.18±1.36% and 98.67±1.40%, respectively. Storage at 40°C showed a reduction to 96.43% in the last week of testing. The data was plotted according to each reaction order equation, and the degree of degradation reaction was determined by the graph that gave a linear form. The degradation rate (k) values were calculated using second-order kinetic models ($R^2 > 0.94$) for all storage conditions. The lowest k value was found in low-temperature storage conditions, followed by room and high temperature with values of 0.003, 0.004, and 0.008/week. Thus, it can be concluded that the preferred storage condition of aripiprazole nanosuspension was at a low temperature (5°C).

CONCLUSION

In conclusion, the aripiprazole nanosuspension, prepared through the combination of high shear homogenization and ultrasonication methods, exhibited favorable characteristics, including small particle size, narrow distribution, and higher drug content. The statistical analysis performed with BBD based on the quadratic model provided valuable insights into the influence of drug concentration, polymer concentration, and polymer ratio on the particle size, PDI, and drug content of the nanosuspension. The results showed that the independent variables significantly affected the characteristics of the nanosuspension. The predicted optimum formula with a desirability of 0.94 was selected and thoroughly evaluated. Furthermore, its characteristic values corresponded to the predicted values, confirming the validity of the regression model.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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