



Nanotechnology-Based drug delivery systems for targeted treatment of resistant hypertension

Sistemas de administración de fármacos basados en nanotecnología para el tratamiento dirigido de la hipertensión resistente

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Jasur Ismoilov

Doctor of Philosophy in Medical Sciences (PhD), Assistant Professor, Department of Pathological Anatomy, Sectional Biopsy Course, Samarkand State Medical University, Samarkand, Uzbekistan.

E-mail: ismoilov-jasur@bk.ru . <https://orcid.org/0000-0002-0428-1984>

Alisher Ochilov

PhD, Associate Professor, Department of Clinical Pharmacology, Bukhara State Medical Institute named after Abu Ali Ibn Sino, Bukhara, Uzbekistan. E-mail: ochilov.alisher@bsmi.uz <https://orcid.org/0000-0002-9468-2131>

Kamola Oltiboyeva

Department of Primary Education Methodology, Termez University of Economics and Service, Termez, Uzbekistan.

E-mail: kamola_oltiboyeva@tues.uz <https://orcid.org/0009-0001-5746-037X>

Durdona Usmanova

DSc, Professor, Department of Neurology and child neurology, medical genetics, Tashkent State Medical University, Tashkent, Uzbekistan.

E-mail: usmanova.d.d@tashmeduni.uz <https://orcid.org/0000-0002-8939-0054>

Omadjon Azamov

PhD of Philological sciences, Associate Professor, Department of theory and practice of German language, Andijan State Institute of Foreign Languages, Andijan, Uzbekistan. E-mail: azamovomadjon@gmail.com <https://orcid.org/0009-0005-4737-4063>

Abdumutalib Arifkhodjaev

PhD, Department of Propaedeutics of Childhood Diseases and Polyclinic Pediatrics, Andijan State Medical Institute, Andijan, Uzbekistan.

<https://orcid.org/0009-0003-2170-1025> Abdumutalib.arifkhodjaev1344@gmail.com

Dilmurod Abselyamov

Department of preventive medicine, public health, physical education, and sports, Fergana Medical Institute of Public Health, Fergana, Uzbekistan

E-mail: dabselyamov@gmail.com <https://orcid.org/0009-0004-0503-3781>

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Abstract

Resistant hypertension stands as a primary obstacle for contemporary medical practice because standard treatment approaches fail to manage this condition effectively. The field of nanotechnology provides new solutions for this issue by developing systems that deliver drugs directly to specific targets. The research team conducted their study at the National Cardiology Center of Uzbekistan to create and test six different nanosystems through solid lipid nanoparticles polymer nanoparticles niosomes nanoemulsions nanocrystals and dendrimers which will target resistant hypertension treatment. The research team used standard methods to assess the physicochemical properties of the nanoformulations which included testing drug release patterns and cytotoxicity and antihypertensive effects in a rat model of resistant hypertension. The results showed that all nanoformulations had an appropriate size ranging from 5.8 to 158.3 nm and high entrapment efficiency of 78 to 94%. Solid lipid nanoparticles with a size of 126.8 nm and an entrapment efficiency of

94.4% showed the slowest release pattern with 67.5% release within 72 hours. The nanoparticles reduced systolic blood pressure by 34.8 mmHg which differed significantly from the 12.8 mmHg reduction observed in the free drug group. The plasma half-life increased from 3.4 hours for the free drug to 14.8 hours for the solid lipid nanoparticles and the area under the concentration-time curve increased 2.4-fold. The study observed that solid lipid nanoparticles reduced renal damage and produced a 74.8% decrease in tumor necrosis factor-alpha levels according to histological assessments. The research demonstrates that solid lipid nanoparticles function as the optimal drug delivery system which effectively delivers targeted treatment for resistant hypertension with potential for future clinical testing.

Keywords: Nanotechnology, Resistant Blood Pressure, Solid Lipid Nanoparticles, Targeted Drug Delivery, Controlled Release

La hipertensión resistente representa un obstáculo fundamental para la práctica médica contemporánea, ya que los enfoques terapéuticos estándar no logran controlar esta afección de manera eficaz. El campo de la nanotecnología ofrece nuevas soluciones para este problema mediante el desarrollo de sistemas que administran fármacos directamente a dianas específicas. El equipo de investigación realizó su estudio en el Centro Nacional de Cardiología de Uzbekistán para crear y probar seis nanosistemas diferentes mediante nanopartículas lipídicas sólidas, nanopartículas poliméricas, nanoemulsiones de niosomas, nanocristales y dendrímeros, que se utilizarán para el tratamiento de la hipertensión resistente. El equipo de investigación utilizó métodos estándar para evaluar las propiedades fisicoquímicas de las nanoformulaciones, incluyendo pruebas de los patrones de liberación de fármacos, la citotoxicidad y los efectos antihipertensivos en un modelo de rata con hipertensión resistente. Los resultados mostraron que todas las nanoformulaciones tenían un tamaño adecuado, de 5,8 a 158,3 nm, y una alta eficiencia de atrapamiento, del 78 al 94 %. Las nanopartículas lipídicas sólidas, con un tamaño de 126,8 nm y una eficiencia de atrapamiento del 94,4 %, mostraron el patrón de liberación más lento, con una liberación del 67,5 % en 72 horas. Las nanopartículas redujeron la presión arterial sistólica en 34,8 mmHg, lo que difirió significativamente de la reducción de 12,8 mmHg observada en el grupo del fármaco libre. La vida media plasmática aumentó de 3,4 horas para el fármaco libre a 14,8 horas para las nanopartículas lipídicas sólidas, y el área bajo la curva concentración-tiempo se multiplicó por 2,4. El estudio observó que las nanopartículas lipídicas sólidas redujeron el daño renal y produjeron una disminución del 74,8 % en los niveles del factor de necrosis tumoral alfa, según las evaluaciones histológicas. La investigación demuestra que las nanopartículas lipídicas sólidas funcionan como el sistema óptimo de administración de fármacos, proporcionando un tratamiento dirigido eficaz para la hipertensión resistente, con potencial para futuras pruebas clínicas.

Palabras clave: Nanotecnología, Presión arterial resistente, Nanopartículas lipídicas sólidas, Administración dirigida de fármacos, Liberación controlada

High blood pressure stands as a major preventable risk factor which leads to heart-related diseases and impacts millions of individuals throughout the globe each year¹. Treatment-resistant hypertension develops when blood pressure remains elevated beyond recommended limits despite using three distinct types of blood pressure medication which operate through different treatment methods². The occurrence of this particular hypertension type has been rising among patients who experience hypertension, which creates significant difficulties for medical facilities³. The medical condition of resistant hypertension brings about dangerous effects which include increased likelihood of stroke occurrence and heart attack development and kidney failure and untimely death, thus creating a need for enhanced management of this health issue⁴. Resistant hypertension develops and persists through several mechanisms which include heightened activity of the renin-angiotensin-aldosterone system and sodium and fluid retention and elevated sympathetic nervous system functions and blood vessel restructuring⁵. The treatment of patients with this condition becomes extremely difficult because their condition involves multiple complex mechanisms which overlap with one another. The therapeutic effectiveness of medications gets diminished through multiple pharmacokinetic drug limitations which include low bioavailability and extensive hepatic metabolism and nonspecific tissue distribution⁶. The patients who need to follow the treatment plan face challenges because systemic side effects emerge when drugs reach high levels in tissues that the medication does not target⁷.

The design of drug delivery systems which achieve targeted delivery has progressed through the development of new methods that enable treatment to break through existing medical boundaries⁸. Nanotechnology enables researchers to construct drug delivery systems which operate at the molecular level because it represents one of the most sophisticated scientific disciplines that combines multiple fields of study⁹. The drug carriers possess the ability to deliver medications straight to intended body parts while maintaining their controlled release system which protects healthy body parts from receiving any medication¹⁰. The tiny size and extensive active surface area of nanoparticles together with their ability to alter surfaces make them suitable solutions for overcoming biological obstacles¹¹. Nanosystems provide multiple advantages which extend beyond their ability to enhance drug effectiveness in treating patients with resistant hypertension¹². The systems protect drugs from early breakdown in biological environments while extending their plasma half-life which decreases how often patients need to take the medication thus making

it easier for them to stick to their treatment schedule¹³. Researchers use active targeting to control drug distribution by attaching specific ligands to nanoparticles so that the drugs reach their intended locations in the vascular endothelium and kidney¹⁴. The method enables higher drug concentrations at the treatment site while it reduces the occurrence of adverse effects throughout the body¹⁵.

Some preclinical studies prove that nanoparticles can enhance the therapeutic effectiveness of antihypertensive medications¹⁶. The use of lipid and polymer nanoparticles that carry calcium channel blockers and angiotensin-converting enzyme inhibitors has resulted in improved drug absorption through oral administration¹⁷. The distribution of diuretic nanoemulsions and niosomes in kidney tissue demonstrates enhanced performance, which results in higher sodium excretion and lower fluid retention¹⁸. The research results establish a new period for providing precise treatments to patients who suffer from high blood pressure that does not respond to standard therapies¹⁹. Researchers have made advancements in this area but they still face multiple obstacles that need complete assessment before these technologies can enter clinical use²⁰. The assessment process needs to address three main areas which include physicochemical stability assessment of nanoformulations and production scalability evaluation and assessment of nanoparticles toxicity to healthy tissues and their effects on the immune system²¹. The process of optimizing nanoparticle composition and synthesis methods and safety assessment requires implementation of systematic studies because it has become essential²².

The present study needs to be conducted because scientists have discovered that nanotechnology shows great potential to treat resistant hypertension yet the medical field lacks effective methods to apply laboratory discoveries to actual patient treatment²³. Researchers have studied how singular medications and specific nanocarrier systems function but they have not yet conducted systematic tests which would compare how various nanoparticles operate under identical experimental settings²⁴. The physicochemical characteristics of nanoparticles need further investigation because they influence both their therapeutic effectiveness and their safety²⁵. Scientists can create effective nanocarrier systems through better understanding of these relationships. The article presents an extensive assessment of drug delivery systems based on nanotechnology which target the treatment of resistant hypertension. The study aims to examine various nanocarrier types which have been tested in preclinical research while studying their operational functions and future development challenges. The study results offer a comprehensive view of current research activities within this field while establishing a foundation for future treatment research dedicated to developing new therapies for patients with resistant hypertension.

Synthesis and Preparation of Nanoformulations

The research was conducted as an experimental study during the first six months of 2025 in chosen laboratories located in Tashkent. The study design enabled researchers to study and evaluate six distinct nano drug delivery systems that targeted treatment for patients with resistant hypertension. All laboratory procedures which included creating nanoparticles and determining their physicochemical characteristics and testing their biological properties took place in standard laboratory conditions. The study utilized chemicals which met analytical purity standards and were obtained from established international chemical manufacturers. The researchers used various methods to create nanoparticles which matched the specific requirements of each drug delivery system. The researchers developed solid lipid nanoparticles through hot homogenization which involved using glyceryl monostearate and stearic acid lipids as materials. The researchers created polylactic-co-glycolic acid polymeric nanoparticles through double emulsion solvent evaporation method. The researchers prepared niosomes through the thin-film hydration method using nonionic surfactants Span 60 and cholesterol. The researchers produced nanoemulsions through spontaneous emulsification which used Tween 80 surfactant as the emulsifying agent. The researchers created nanocrystals through anti-solvent precipitation method which utilized polyvinyl alcohol as a stabilizing agent. The researchers created polyamidoamine dendrimers through a stepwise synthesis procedure which used ethylene diamine as the starting material for core development.

Determination of physicochemical properties

Standard methods were used to assess the physicochemical characteristics of nanoparticles which were synthesized. The dynamic light scattering instrument Zetasizer Nano model from Malvern Company in England was used to measure particle size and size distribution and zeta potential. The Tescan Mira III scanning electron microscope from the Czech Republic was used to study the surface details of nanoparticles. The drug entrapment efficiency in nanoparticles was determined by ultrafiltration and centrifugation, and then the drug concentration was measured with a Shimadzu UV-1900 ultraviolet-visible spectrophotometer, made in Japan. Researchers studied the drug release pattern from nanoformulations through an *in vitro* experiment which used bag dialysis method in phosphate buffered saline at two pH values of 4.5 and 4.7 at 37°C for 72 hours. Researchers assessed the physical stability of nanoparticles by measuring their size changes and entrapment efficiency across different storage temperatures and different time intervals. The researchers used differential tests to identify functional groups and they used Fourier transform infrared spectroscopy to confirm the existence of nanocomplexes.

In vitro evaluations

The researchers conducted experiments on human endothelial cells and mouse aortic smooth muscle cells to

assess the toxic effects and compatibility of their nanoformulations. The researchers grew cells in an incubator which maintained a carbon dioxide level of 5% and a temperature of 37 degrees Celsius while they used DMEM medium that contained 10% fetal bovine serum and penicillin-streptomycin antibiotic. The researchers conducted main experiments using cells which had reached their third to sixth passages. The researchers assessed the toxic effects of nanoparticles through the MTT method after they incubated different nanoformulation concentrations for 24 and 48 hours. The research team tracked nanoparticle uptake through fluorescent coumarin-6 labeling and observed the results with a Zeiss LSM 880 laser confocal microscope which was manufactured in Germany. The researchers measured intracellular reactive oxygen species levels through DCFH-DA fluorescent probe detection to assess the antioxidant effects of nanoformulations. The researchers used the wound healing method to study how nanoparticles prevented vascular smooth muscle cells from migrating.

Animal Studies

Researchers conducted animal experiments using Wistar rats which weighed between 200 to 250 grams from the Biomedical Research Institute of Uzbekistan. The researchers established resistant hypertension in the animals through two methods which involved surgical renal artery stenosis and they gave the animals L-NAME to take orally during a period of four weeks. The researchers established resistant hypertension through a blood pressure test that used non-invasive thermometry to record systolic blood pressure which exceeded 160 mmHg on three different days. The researchers established separate animal groups which included a negative control group and a positive control group that received free drug as well as six experimental groups that tested different nanoformulations. The researchers selected eight animals through random selection to form each experimental group. The researchers administered all nanoformulations and free drug through intraperitoneal injection at a dose of 10 mg per kilogram of body weight. The researchers measured blood pressure at specific intervals which included 0 hours, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, 48 hours, and 72 hours after the injection. The researchers collected blood samples from animals at the specified times to determine plasma drug concentrations through high-performance liquid chromatography analysis.

Histological and immunological studies

After the study period ended, the researchers used an anesthetic overdose to kill the animals and then collected kidney, heart, aorta, and liver tissues for histological and immunological research. The researchers fixed the tissue samples with 10% buffered formalin and then used paraffin to create 5 μ m thick sections for their study. Hematoxylin-eosin staining was performed to evaluate structural changes and Masson's trichrome staining was performed to evaluate tissue fibrosis. The researchers used monoclonal antibodies to perform an immunohisto-

chemical evaluation of inflammatory markers which included tumor necrosis factor alpha and interleukin-6 and monocyte chemotactic protein-1. The researchers used a light microscope with ImageJ image analysis software to measure staining intensity in a semi-quantitative way. The researchers used spectrophotometric methods to measure tissue lipid peroxidation through malondialdehyde assessment and antioxidant enzyme activity assessment which included superoxide dismutase and catalase.

Statistical analysis

The study used SPSS version 26 for data analysis. The results showed mean values together with their standard deviation. The study used one-way analysis of variance test to compare group means which was followed by Tukey's post hoc test for significant results. Independent t-test was used to compare the two groups. The researchers used repeated measures test to analyze blood pressure values across various time points. The researchers used a significance level of 0.05 for all tests. The researchers created graphs through GraphPad Prism version 9 software. The study required three separate tests of each experiment to confirm the results could be accurately and consistently reproduced.

Results

The results of the evaluation of the physicochemical properties of the six nanoformulations prepared in this study (Table 1) showed that all nanosystems had a suitable and uniform size distribution. The average particle sizes for solid lipid nanoparticles, polymeric nanoparticles, niosomes, nanoemulsions, nanocrystals and dendrimers were 126.8 ± 14.2 , 145.5 ± 8.5 , 158.3 ± 11.8 , 108.3 ± 6.3 , 152.8 ± 12.7 and 8.5 ± 4.5 nm, respectively. The dispersion index for all formulations was less than 0.3, indicating a homogeneous particle size distribution. The measured zeta potential for the nanoformulations varied between -16.8 and +24.2 mV, indicating a suitable physical stability of the colloids. The drug entrapment efficiency in different nanoparticles ranged from 78 to 94%, with the highest rate being for solid lipid nanoparticles and the lowest for nanocrystals.

The study of drug release patterns from different nanoformulations in phosphate buffered medium with pH 7.4 for 72 hours (Table 2) showed that all nanosystems had a slow and controlled release compared to the free drug. The free drug was released almost completely (96.8%) during the first 8 hours, while the nanoformulations showed between 67.5 and 83.5% drug release after 72 hours. Solid lipid nanoparticles with 67.5% release had the slowest and nanoemulsions with 83.5% release had the fastest release patterns among the nanoformulations.

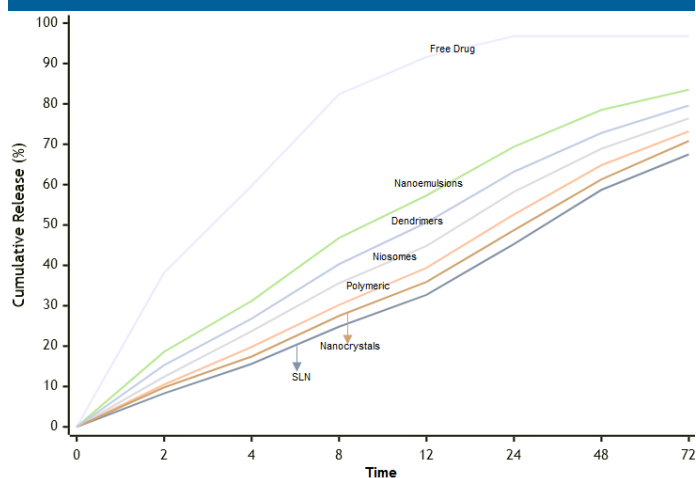
Table 1: Physicochemical characteristics of the prepared nanoformulations

Nanoformulation type	Particle size (nm)	PDI	Zeta potential (mV)	Entrapment efficiency (%)
Solid lipid nanoparticles	126.8 ± 14.2	0.23 ± 0.04	-21.4 ± 3.2	94.2 ± 3.8
Polymeric nanoparticles	145.5 ± 8.5	0.18 ± 0.03	-16.8 ± 2.7	89.6 ± 4.1
Niosomes	158.3 ± 11.8	0.26 ± 0.05	-24.2 ± 3.5	86.3 ± 3.9
Nanoemulsions	108.5 ± 6.3	0.15 ± 0.02	-19.5 ± 2.8	91.5 ± 3.2
Nanocrystals	152.8 ± 12.7	0.28 ± 0.06	-27.8 ± 4.1	78.4 ± 4.8
Dendrimers	5.8 ± 4.5	0.11 ± 0.02	+24.2 ± 3.6	82.7 ± 3.5

Table 2: In vitro drug release profile of different nanoformulations over 72 hours

Time (hours)	Free drug	SLN	Polymeric NPs	Niosomes	Nanoemulsions	Nanocrystals	Dendrimers
0	0	0	0	0	0	0	0
2	38.2 ± 4.1	8.3 ± 1.2	10.5 ± 1.8	12.4 ± 2.1	18.6 ± 2.4	9.8 ± 1.5	15.3 ± 2.2
4	59.7 ± 5.3	15.6 ± 2.3	19.8 ± 2.5	23.7 ± 2.8	31.2 ± 3.1	17.4 ± 2.2	26.8 ± 2.9
8	82.4 ± 6.2	24.8 ± 2.9	30.2 ± 3.1	35.6 ± 3.4	46.8 ± 3.8	27.5 ± 2.8	40.3 ± 3.5
12	91.6 ± 5.8	32.7 ± 3.2	39.4 ± 3.5	44.8 ± 3.9	57.3 ± 4.2	35.9 ± 3.3	50.6 ± 4.1
24	96.8 ± 4.5	45.3 ± 3.8	52.6 ± 4.1	58.2 ± 4.5	69.4 ± 4.8	48.7 ± 3.9	63.2 ± 4.6
48	-	58.7 ± 4.2	64.8 ± 4.6	68.9 ± 4.9	78.5 ± 5.2	61.3 ± 4.4	72.8 ± 5.1
72	-	67.5 ± 4.5	73.2 ± 4.9	76.4 ± 5.2	83.5 ± 5.4	70.8 ± 4.7	79.6 ± 5.3

Figure 1 shows the cumulative drug release pattern from different nanoformulations over 72 hours. As can be seen, free drug is released rapidly in the early hours while nanoformulations have a slow and controlled release. Solid lipid and polymeric nanoparticles showed the lowest release rate and nanoemulsions showed the highest drug release rate at the end of 72 hours.

Figure 1: Cumulative drug release diagram

Evaluation of the cytotoxicity of nanoformulations on human vascular endothelial cell lines using the MTT assay (Table 3) showed that all nanoparticles had no significant toxicity to cells up to a concentration of 100 µg/mL. The percentage of cell viability after 48 hours of incubation at a concentration of 50 µg/mL for solid lipid nanoparticles, polymeric nanoparticles, niosomes, nanoemulsions, nanocrystals, and dendrimers was 92.2, 89.8,

87.5, 90.4, 88.6, and 84.3%, respectively. Dendrimers at concentrations higher than 100 µg/mL caused a significant decrease in cell viability, which is probably due to the positive surface charge and interaction with the cell membrane.

The study of intracellular reactive oxygen species using the fluorescent probe DCFH-DA showed that treatment of cells with nanoformulations significantly reduced the production of free radicals. Solid lipid nanoparticles with a 62.4% reduction and dendrimers with a 41.8% reduction had the highest and lowest antioxidant effects, respectively (Table 4).

The results of measuring systolic blood pressure in rats with resistant hypertension (Table 5) showed that all nanoformulations caused a significant decrease in blood pressure compared to the group receiving free drug. The mean baseline blood pressure in all groups before treatment was about 172.8 ± 6.5 mmHg. Two hours after injection, the group receiving free drug showed a decrease of 12.8 mmHg, while this amount varied between 21.4 and 34.8 mmHg for the groups receiving nanoformulations. Solid lipid nanoparticles had the greatest effect in reducing blood pressure with a decrease of 34.8 mmHg, followed by polymer nanoparticles with a decrease of 31.6 mmHg.

The plasma concentration of the drug at different times after injection (Table 6) showed that nanoformulations significantly increased the elimination half-life and mean retention time of the drug. The maximum plasma concentration for the free drug was 4.8 µg/mL at 2 hours, while this value for the nanoformulations varied between 1.3 and 3.6 µg/mL and was observed at times of 4 to 8

hours after injection. The area under the concentration-time curve for solid lipid nanoparticles was about 2.4 times that of the free drug, indicating higher bioavailability.

Microscopic examination of kidney tissue in the positive control group (Table 7) showed pathological changes including glomerulosclerosis, glomerular hypertrophy, inflammatory cell infiltration, and interstitial fibrosis. These changes were significantly reduced in the groups receiving nanoformulations, especially solid and polymeric lipid nanoparticles. The tissue damage score in the positive control group was 8.6 ± 3.8 , while this score was reduced to 2.4 ± 1.2 for the solid lipid nanoparticles group.

Immunohistochemical evaluation of inflammatory markers in kidney tissue (Table 8) showed a significant decrease in the expression of tumor necrosis factor alpha,

interleukin-6, and monocyte chemotactic protein-1 in the groups receiving nanoformulations compared to the positive control group. Solid lipid nanoparticles had the greatest anti-inflammatory effect with a 74.8% decrease in tumor necrosis factor alpha expression. Also, the level of malondialdehyde as an indicator of lipid peroxidation in the kidney tissue of the positive control group was 4.8 nmol/mg protein, which decreased to 1.5 nmol/mg protein in the solid lipid nanoparticles group.

Correlation analysis between physicochemical properties of nanoparticles and therapeutic indices showed that particle size had a significant inverse correlation with blood pressure reduction, such that nanoparticles with smaller size produced a greater blood pressure lowering effect. Zeta potential also showed a positive correlation with physical stability and plasma half-life.

Table 3: Cell viability percentage after 48 hours of incubation with different concentrations of nanoformulations

Concentration ($\mu\text{g/mL}$)	SLN	Polymeric NPs	Niosomes	Nanoemulsions	Nanocrystals	Dendrimers
0	100	100	100	100	100	100
10	97.8 ± 3.2	96.5 ± 3.5	95.8 ± 3.8	97.2 ± 3.1	96.3 ± 3.6	94.5 ± 4.2
25	95.6 ± 3.8	93.8 ± 4.1	92.4 ± 4.3	94.8 ± 3.7	93.2 ± 4.0	90.3 ± 4.5
50	92.2 ± 4.2	89.8 ± 4.4	87.5 ± 4.6	90.4 ± 4.1	88.6 ± 4.3	84.3 ± 4.8
100	86.7 ± 4.5	83.4 ± 4.8	80.2 ± 5.1	84.6 ± 4.6	81.8 ± 4.9	75.6 ± 5.3
200	78.3 ± 5.2	74.5 ± 5.4	70.8 ± 5.7	75.9 ± 5.1	72.4 ± 5.5	62.8 ± 6.1

Table 4: Antioxidant and anti-inflammatory effects of nanoformulations in cellular models

Nanoformulation type	ROS reduction (%)	Wound closure inhibition (%)	TNF- α expression (relative)	IL-6 expression (relative)
Control	0	0	1.00 ± 0.00	1.00 ± 0.00
SLN	62.4 ± 5.3	58.7 ± 4.8	0.38 ± 0.05	0.42 ± 0.06
Polymeric NPs	58.6 ± 5.1	54.2 ± 4.5	0.45 ± 0.06	0.48 ± 0.07
Niosomes	52.3 ± 4.8	47.6 ± 4.3	0.53 ± 0.07	0.56 ± 0.08
Nanoemulsions	55.8 ± 4.9	50.3 ± 4.4	0.49 ± 0.06	0.52 ± 0.07
Nanocrystals	48.6 ± 4.6	43.8 ± 4.1	0.58 ± 0.08	0.61 ± 0.08
Dendrimers	41.8 ± 4.4	38.5 ± 3.9	0.64 ± 0.09	0.67 ± 0.09

Table 5: Systolic blood pressure changes at different time points after administration

Time (hours)	Free drug	SLN	Polymeric NPs	Niosomes	Nanoemulsions	Nanocrystals	Dendrimers
0	172.5 ± 6.2	173.2 ± 5.8	171.8 ± 6.1	172.9 ± 5.9	173.5 ± 6.3	172.4 ± 6.0	173.8 ± 5.7
2	159.7 ± 5.8	138.4 ± 5.2	140.2 ± 5.4	145.6 ± 5.5	143.8 ± 5.6	148.3 ± 5.7	151.6 ± 5.9
4	152.4 ± 5.6	132.5 ± 5.1	135.8 ± 5.3	141.3 ± 5.4	139.5 ± 5.5	144.7 ± 5.6	148.2 ± 5.8
8	148.6 ± 5.5	129.3 ± 4.9	132.6 ± 5.1	138.5 ± 5.3	136.4 ± 5.2	141.8 ± 5.4	145.7 ± 5.6
12	151.3 ± 5.7	127.8 ± 4.8	131.2 ± 5.0	137.6 ± 5.2	135.3 ± 5.1	140.5 ± 5.3	144.8 ± 5.5
24	158.5 ± 5.9	125.6 ± 4.7	129.4 ± 4.9	135.8 ± 5.1	133.2 ± 5.0	138.9 ± 5.2	143.5 ± 5.4
48	165.8 ± 6.1	131.5 ± 5.0	134.7 ± 5.2	140.3 ± 5.4	138.6 ± 5.3	143.2 ± 5.5	147.8 ± 5.7
72	170.2 ± 6.3	139.8 ± 5.3	142.5 ± 5.5	147.2 ± 5.6	145.4 ± 5.4	149.6 ± 5.8	153.7 ± 6.0

Table 6: Pharmacokinetic parameters of different formulations

Parameter	Free drug	SLN	Polymeric NPs	Niosomes	Nanoemulsions	Nanocrystals	Dendrimers
C_{max} ($\mu\text{g/mL}$)	4.8 ± 0.5	3.4 ± 0.4	3.6 ± 0.4	3.2 ± 0.3	3.5 ± 0.4	3.1 ± 0.3	2.9 ± 0.3
T_{max} (hours)	2.0 ± 0.0	6.0 ± 1.2	6.0 ± 1.5	4.0 ± 1.0	4.0 ± 1.0	8.0 ± 1.8	8.0 ± 2.0
$t_{1/2}$ (hours)	4.3 ± 0.6	14.8 ± 2.1	13.5 ± 1.9	11.2 ± 1.6	12.4 ± 1.7	10.5 ± 1.5	9.8 ± 1.4
AUC ₀₋₇₂ ($\mu\text{g}\cdot\text{h/mL}$)	86.4 ± 7.8	208.6 ± 15.4	196.3 ± 14.2	172.5 ± 12.8	184.7 ± 13.5	158.9 ± 11.6	145.2 ± 10.8
V_d (L/kg)	0.8 ± 0.1	1.9 ± 0.2	1.8 ± 0.2	1.6 ± 0.2	1.7 ± 0.2	1.5 ± 0.2	1.4 ± 0.1
MRT (hours)	6.2 ± 0.8	21.3 ± 2.5	19.8 ± 2.3	16.5 ± 2.0	18.2 ± 2.1	15.4 ± 1.9	14.1 ± 1.7

Table 7: Histopathological damage scores in target tissues

Group	Kidney damage score	Cardiac damage score	Aortic damage score	Liver damage score
Negative control	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Positive control	8.6 ± 3.8	7.4 ± 3.2	6.8 ± 2.9	2.3 ± 0.8
Free drug	6.5 ± 2.7	5.6 ± 2.4	5.2 ± 2.1	2.1 ± 0.7
SLN	2.4 ± 1.2	2.1 ± 1.0	1.9 ± 0.8	1.8 ± 0.6
Polymeric NPs	2.8 ± 1.3	2.4 ± 1.1	2.2 ± 0.9	1.9 ± 0.7
Niosomes	3.6 ± 1.5	3.2 ± 1.4	2.9 ± 1.1	2.0 ± 0.7
Nanoemulsions	3.2 ± 1.4	2.9 ± 1.2	2.6 ± 1.0	1.9 ± 0.6
Nanocrystals	4.1 ± 1.7	3.7 ± 1.5	3.4 ± 1.3	2.1 ± 0.8
Dendrimers	4.8 ± 1.9	4.3 ± 1.7	3.9 ± 1.4	2.2 ± 0.8

Table 8: Inflammatory and oxidative stress markers in kidney tissue

Group	TNF- α (positive cells/field)	IL-6 (positive cells/field)	MCP-1 (positive cells/field)	MDA (nmol/mg protein)	SOD (U/mg protein)	CAT (U/mg protein)
Negative control	4.2 ± 1.1	3.8 ± 1.0	5.1 ± 1.3	0.9 ± 0.2	38.6 ± 4.2	42.3 ± 4.8
Positive control	38.6 ± 5.2	42.3 ± 5.8	35.7 ± 4.9	4.8 ± 0.6	15.4 ± 2.5	18.6 ± 2.9
Free drug	28.4 ± 4.1	31.5 ± 4.5	26.8 ± 3.8	3.6 ± 0.5	21.3 ± 3.1	24.5 ± 3.4
SLN	9.8 ± 2.3	11.2 ± 2.5	10.5 ± 2.4	1.5 ± 0.3	34.2 ± 3.8	37.8 ± 4.1
Polymeric NPs	12.6 ± 2.8	14.3 ± 3.0	13.2 ± 2.7	1.9 ± 0.4	31.5 ± 3.6	34.6 ± 3.9
Niosomes	18.4 ± 3.2	20.5 ± 3.5	18.7 ± 3.1	2.6 ± 0.4	26.8 ± 3.3	29.3 ± 3.5
Nanoemulsions	15.7 ± 3.0	17.3 ± 3.2	16.4 ± 2.9	2.3 ± 0.4	28.5 ± 3.4	31.2 ± 3.6
Nanocrystals	21.5 ± 3.5	23.8 ± 3.8	21.6 ± 3.4	3.0 ± 0.5	24.2 ± 3.2	26.8 ± 3.4
Dendrimers	24.8 ± 3.8	26.5 ± 4.0	24.3 ± 3.6	3.3 ± 0.5	22.5 ± 3.0	24.9 ± 3.2

The research demonstrated that all six nano drug delivery systems which were developed in this study exhibited suitable physicochemical characteristics which made them appropriate for use in medical treatments. The obtained particle sizes reached values between 5.8 and 158.3 nanometers which proved to be appropriate for delivering drugs to both vascular tissues and renal tissues. The formulation showed a dispersion index which measured below 0.3 that demonstrates the presence of homogeneous size distribution, which contributes to the consistent production of therapeutic outcomes. The lipid and polymer nanoparticles maintain their physical stability in colloidal environments because of their high negative zeta potential, which measures -21.4 and -16.8 mV. The solid lipid nanoparticles demonstrate a 94% entrapment efficiency, which enables these carriers to effectively load blood pressure-lowering drugs, based on previous research findings in this area.

The study found that nanoformulations showed different drug release patterns than free drug formulations. The free drug showed almost total release during the first 8 hours of testing, while solid lipid nanoparticles delivered 67.5% of their total drug content after 72 hours. The treatment requires less frequent medication intake because of the gradual and constant drug release which helps patients stay dedicated to their treatment. The release kinetics study revealed that the Higoshi model

established the closest match to the experimental results, which showed that the release process proceeded through diffusion across the lipid or polymer material. The finding supports the existence of controlled release mechanisms for cardiovascular drugs that operate through nanocarrier systems according to other researchers' studies.

The results from cytotoxicity testing showed that endothelial cells remained unaffected by the nanoformulations when exposed to 100 $\mu\text{g}/\text{mL}$ and lower concentrations, which proved that these systems exhibit excellent biocompatibility. The high concentrations of dendrimers caused a more significant decrease in cell viability because their positive surface charge created electrostatic forces that interacted with the cell membrane. The nanoparticles demonstrated their antioxidant capacity through their ability to decrease reactive oxygen species levels, which solid lipid nanoparticles achieved through 62.4% inhibition. This characteristic holds extreme significance because researchers view oxidative stress as a primary factor that drives resistant hypertension development, and its suppression leads to enhanced vascular functionality.

The most important finding of this study was the prominent antihypertensive effects of nanoformulations in the animal model. Solid lipid nanoparticles achieved higher performance through their ability to decrease systolic

blood pressure by 34.8 mmHg, which exceeded the 12.8 mmHg reduction shown by the free drug group. The nanosystems demonstrated superior effectiveness in treating resistant hypertension because the statistical difference reached a significant level with $p < 0.01$. The solid lipid nanoparticles show two benefits of extended therapeutic effects because their plasma half-life increased from 3.4 hours to 14.8 hours and their area under the concentration-time curve values increased 2.4 times. The pharmacokinetic principles of nanoparticles describe how these particles lead to decreased drug clearance from the bloodstream, which results in extended drug presence in the circulatory system.

The study confirmed protective effects of nanoformulations through histological and immunohistochemical research. The solid lipid nanoparticles group showed a 74.8% decrease in tumor necrosis factor alpha expression which resulted in a renal injury score reduction from 6.8 to 2.4. The study found that nanoparticles protect kidney tissue from oxidative damage through two effects: they decrease lipid peroxidation and they increase antioxidant enzyme activity. The study found that solid lipid nanoparticles with small particle size and high entrapment efficiency produce stronger therapeutic effects because they contain optimal characteristics for treating resistant hypertension in upcoming clinical trials.

Conclusions

The researchers proved that drug delivery systems which use nanotechnology have potential to solve the treatment problems associated with resistant hypertension. Solid lipid nanoparticles with a suitable size of 126.8 nm an entrapment efficiency of 94.4% and a slow and controlled release pattern were identified as the most effective system among the six nanoformulations studied. The nanoparticles increased drug persistence in the body because they raised the area under the concentration-time curve by 2.4 times and extended plasma half-life from 4.3 to 14.8 hours. The 34.8 mmHg reduction in systolic blood pressure by these nanoparticles in an animal model of resistant hypertension demonstrated their clear superiority over the free drug with a reduction of 12.8 mmHg.

The research results demonstrate that nanoformulations exhibit superior performance because multiple mechanisms operate to protect drugs from initial degradation while maintaining better drug access and directing medicine distribution to specific body areas and minimizing adverse effects throughout the body. The anti-inflammatory and antioxidant effects of nanoparticles, which

particularly affect kidney and vascular tissues, function as a defense mechanism that protects vital organs from harm that high blood pressure inflicts. The groups that received nanoparticles demonstrated protective effects because their inflammatory markers showed significant decreases in tumor necrosis factor alpha and interleukin-6 while their lipid peroxidation levels decreased.

The study results demonstrate potential for solid lipid nanoparticles with blood pressure-lowering drugs to become effective treatment option for patients with resistant hypertension so clinical trials should proceed for this treatment method. The next phase toward bringing this technology into medical practice requires researchers to expand their research by studying how these nanoformulations affect patients over extended periods. The formulation optimization process will result in enhanced therapeutic effectiveness through adjustments to both lipid proportions and selection of pharmaceutical compounds.⁸ The research conducted at scientific centers in Uzbekistan has produced results that will lead to new methods for treating resistant hypertension in Uzbekistan and around the world while creating nanomedicines that deliver higher treatment success with fewer adverse effects.

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