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FORMULATION DEVELOPMENT AND EVALUATION OF RESVERATROL LOADED METAL OXIDE NANOPARTICLES

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Abstract:
The present investigation focused on the synthesis, characterization, and evaluation of Resveratrol-loaded copper oxide nanoparticles (CuO-NPs). Resveratrol, identified as an off-white, bitter, amorphous solid, exhibited a melting point of 259–260 °C and demonstrated solubility in phosphate buffer (pH 6.8), 0.1N HCl, methanol, and ethanol, with limited solubility in water. Its partition coefficient (Log P = 8.875) indicated moderate lipophilicity, and UV spectroscopic analysis revealed a maximum absorption wavelength at 304 nm. A calibration curve prepared in phosphate buffer (pH 6.8) showed linearity in the range of 10–50 µg/ml with a correlation coefficient of 0.995. Compatibility studies confirmed suitability of selected excipients for nanoparticle formulation. Five formulations (DCN-1 to DCN-5) of Resveratrol-loaded CuO-NPs were synthesized using varying drug-to-copper nitrate ratios, with optimized stirring conditions of 800 rpm for 3 hours. The percentage yield ranged between 58.21–66.71%. Particle size analysis revealed nanoparticles in the range of 90 ± 9 to 142 ± 16 nm with polydispersity indices of 0.198–0.247 and zeta potential values below –3.05, indicating stability. Drug entrapment efficiencies varied from 29.38–48.28%, decreasing at extreme copper nitrate concentrations. SEM analysis of the optimized formulation (DCN-3) confirmed irregular surface morphology. In-vitro drug release studies demonstrated that DCN-3 exhibited the highest release (93.42%), and kinetic modeling suggested that the release mechanism followed the Peppas–Korsmeyer model, indicating diffusion-controlled kinetics with possible polymer relaxation or erosion. Overall, the study highlights the potential of CuO-NPs as a promising carrier system for enhancing the bioavailability and controlled release of Resveratrol.

Keywords: *Nanocarrier, Copper Oxide, Resveratrol, Metal Oxide, Nanoparticles, Natural*

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INTRODUCTION:

The research focuses on developing a novel nanocarrier system that enhances the therapeutic potential of Resveratrol, a natural polyphenolic compound known for its antioxidant, anti-inflammatory, and anticancer properties but limited by poor bioavailability[1]. The study will begin with the synthesis of CuO nanoparticles using either chemical or green synthesis methods to achieve controlled particle size and morphology suitable for drug loading[2]. Resveratrol will then be incorporated into these nanoparticles through adsorption or encapsulation techniques, and the efficiency of drug loading will be evaluated[3]. Comprehensive characterization will be carried out using SEM, TEM, FTIR, zeta potential, and thermal analysis to confirm structural, morphological, and surface properties[4]. *In-vitro* drug release studies will be performed to assess the controlled release behavior of Resveratrol from the CuO nanocarrier[5]. Biological investigations can include antioxidant assays, antimicrobial testing against bacterial and fungal strains, and cytotoxicity studies on cancer cell lines to evaluate the synergistic therapeutic effects of Resveratrol and CuO[6]. The expected outcome of this research is the development of a dual-functional nanoplatform that not only enhances resveratrol's pharmacological activity but also leverages the inherent activity and catalytic properties of CuO nanoparticles, thereby contributing to innovative strategies in nanomedicine and drug delivery.

Metal oxide NPs can be conjugated with small molecule drugs, proteins, enzymes, antibodies, nucleotides, and genes to deliver them to target organs or cells[7]. Copper nanoparticles have shown potential in various therapies, including chemodynamic therapy, phototherapy, hyperthermia, and immunotherapy[8]. They are also being investigated for their dual diagnostic and therapeutic applications[9]. Copper-containing nanoparticles have antimicrobial properties and can be used in dentistry to inhibit pathogenic microorganisms[10].

Hence, the objective of the present investigation is to synthesize, characterize and investigate the Resveratrol loaded Copper oxide nanoparticles (CuO-NPs).

MATERIALS AND METHODS:

Formulation of Resveratrol Loaded Copper Oxide Nanoparticles (CuO-NPs): Resveratrol-loaded Copper Oxide Nanoparticles (CuO-NPs) represent a cutting-edge approach to improve the potency of Resveratrol with the unique properties of CuO nanoparticles.

Method of formulation of CuO-NPs: Copper salt, copper nitrate was dissolved in distilled water. The pH was adjusted by slowly adding NaOH to initiate precipitation of CuO. Surfactant Tween 80 was added during precipitation as stabilizing agent for dispersion, prevention of aggregation and also controls particle size. Continuously stirred the solution and applied sonication to reduce particle size until optimum size obtained size range 10–100 nm was targeted for optimal cellular uptake. The obtained suspension was centrifuged at 8000 rpm and the precipitate washed, then dried, CuO-NPs were obtained.

Drug loading (incorporation of Resveratrol): Resveratrol was dissolved in ethanol. Drug solution was mixed with CuO-NPs under ultrasonication then magnetic stirring. Dispersion was enhanced by using surfactants Poloxamer 407.
Lyophilization (Freeze-Drying): The nanoparticle suspension was freezed. Dry Resveratrol-loaded CuO-NPs were obtained by Lyophilization.

Composition of Resveratrol Loaded Copper Oxide Nanoparticles (CuO-NPs): Total five Resveratrol-loaded copper oxide nanoparticles (DCN-1 to DCN-5) were prepared using different ratio of drug and copper nitrate. The synthesis of Resveratrol-loaded copper oxide nanoparticles (CuO NPs), stirring speed plays a crucial role in controlling particle size, dispersion and homogeneity hence optimized stirring speed was 800 rpm for 3 hours.

Table No. 1: Composition of Resveratrol loaded copper oxide nanoparticles

S. No.	Ingredients	DCN-1	DCN-2	DCN-3	DCN-4	DCN-5
1	Copper nitrate (0.1 M)	50 ml	100 ml	150 ml	200 ml	250 ml
2	Tween 80	15 mg	15 mg	15 mg	15 mg	15 mg
3	NaOH (0.8M)	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
4	Stirring speed (rpm)	800	800	800	800	800
5	Resveratrol in ethanol	100 mg	100 mg	100 mg	100 mg	100 mg
6	Poloxamer 407	6 mg	6 mg	6 mg	6 mg	6 mg

RESULT AND DISCUSSION:

Preformulation study:

The present investigation was to synthesize, characterize and investigate the Resveratrol loaded Copper oxide nanoparticles (CuO-NPs). The drug sample was examined for its color, odor, taste etc. the Resveratrol was off white, characteristic, bitter and amorphous solid. The melting point of Resveratrol was observed in the range of 259 to 260 ^{O}C starts to melt. The solubility of Resveratrol in various mediums was studied. Resveratrol was soluble in Phosphate buffer pH 6.8 and 0.1N HCl, freely soluble in methanol and ethanol, slightly soluble in water. The partition coefficient (Log P) of Resveratrol was observed as 8.875 indicating moderate lipophilicity. Determination of wavelength using UV spectroscopy: The maximum wavelength of Resveratrol was found to be 304 nm. A calibration curve of Resveratrol in Phosphate buffer pH 6.8 was prepared in linearity range of 10-50 µg/ml with regression equation (0.011x + 0.008) and correlation coefficient (0.995). The drug (Resveratrol) was found to be compatible with various excipients which were selected for formulation of CuO-NPs.

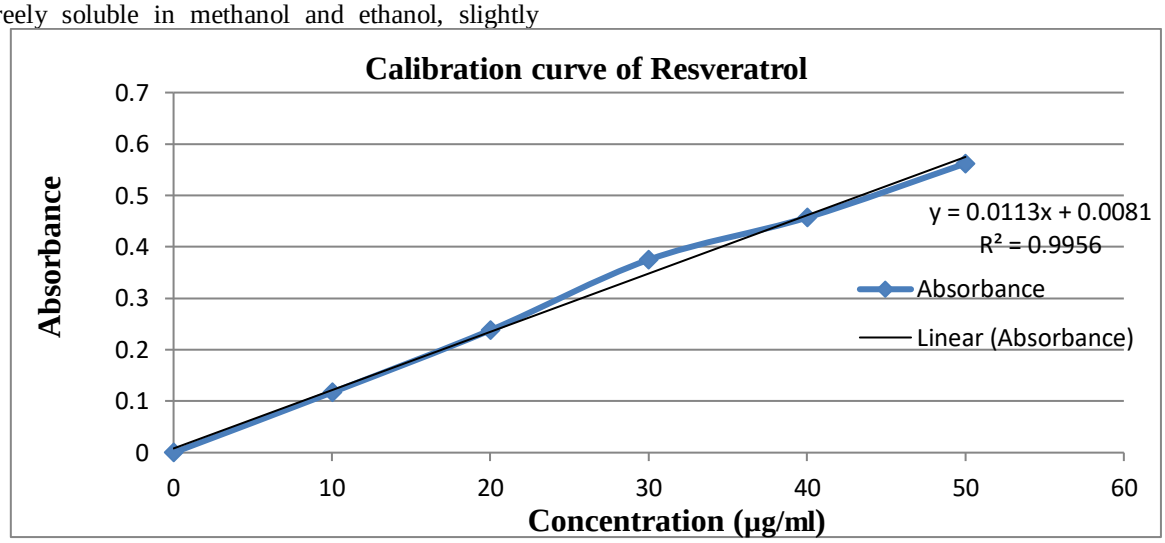

Figure 1: Calibration graph of Resveratrol in 6.8 pH phosphate buffer at 304 nm

Resveratrol Loaded Copper Oxide Nanoparticles (CuO-NPs):

Total five Resveratrol-loaded copper oxide nanoparticles (DCN-1 to DCN-5) were prepared using different ratio of drug and copper nitrate. The synthesis of Resveratrol-loaded copper oxide nanoparticles (CuO NPs), stirring speed plays a crucial role in controlling particle size, dispersion and homogeneity hence optimized stirring speed was 800 rpm for 3 hours.

Evaluation of Resveratrol Loaded Copper Oxide Nanoparticles (CuO-NPs):

Evaluation of Resveratrol loaded copper oxide nanoparticles (CuO-NPs) was performed and found. Percentage yield of various formulations were determined by weighing the CuO-NPs after freeze drying. The (%) yield of different formulations was found in range of 58.21 - 66.71%. Particle size was determined by zeta sizer having role in absorption and bioavailability of drug. Average particle size of Resveratrol loaded CuO-NPs was in range (90 ± 09) to (142 ± 16) nm, PDI in (0.198 ± 0.02) to (0.247 ± 0.02) and potential was found more than (-3.05). Drug entrapment efficacies of various formulations were in range of 29.38 to 48.28 %. Drug entrapment efficacies decrease at higher and lower concentration of copper nitrate solution. Surface of the CuO-NPs were irregular in shape and size as observed in the microphotograph of optimized formulation DCN-3 taken by SEM.

Table No. 2: Evaluation of Resveratrol Loaded Copper Oxide Nanoparticles (CuO-NPs)

S. No	Formulation code	Percent Yield (%)	Size average (nm)	PDI (mean)	Zeta Potential (mV)	Drug entrapment (%)
1	DCN-1	63.71	110 ± 17	0.237 ± 0.01	-3.35 ± 0.12	31.28 %
2	DCN-2	64.23	102 ± 12	0.214 ± 0.03	-3.12 ± 0.14	34.28 %
3	DCN-3	66.71	90 ± 09	0.198 ± 0.02	-3.14 ± 0.11	48.28 %
4	DCN-4	62.37	120 ± 11	0.235 ± 0.01	-3.28 ± 0.09	37.18 %
5	DCN-5	58.21	142 ± 16	0.247 ± 0.02	-3.05 ±0.06	29.38 %

***In-vitro* release studies**

In-vitro (%) drug release study of Resveratrol loaded CuO-NPs was performed and found that the Resveratrol loaded CuO-NPs DCN-3 have higher percentage of drug release i.e. 93.42%, so the DCN-3 drug release data was modified for kinetic modeling.

Table No. 3: *In-vitro* (%) drug release study of Resveratrol loaded CuO-NPs

Time (hr)	DCN-1	DCN-2	DCN-3	DCN-4	DCN-5
0.0	0	0	0	0	0
1.0	35.03	33.11	36.22	24.43	23.15
2.0	46.25	42.17	43.28	36.76	35.12
3.0	54.65	56.73	48.68	46.42	47.16
4.0	62.75	62.91	58.44	52.37	56.76
6.0	73.17	71.17	69.91	67.37	68.57
8.0	81.52	80.42	76.17	73.17	78.41
12.0	83.31	86.61	85.38	79.13	81.37
16.0	84.55	88.48	93.42	81.15	82.22

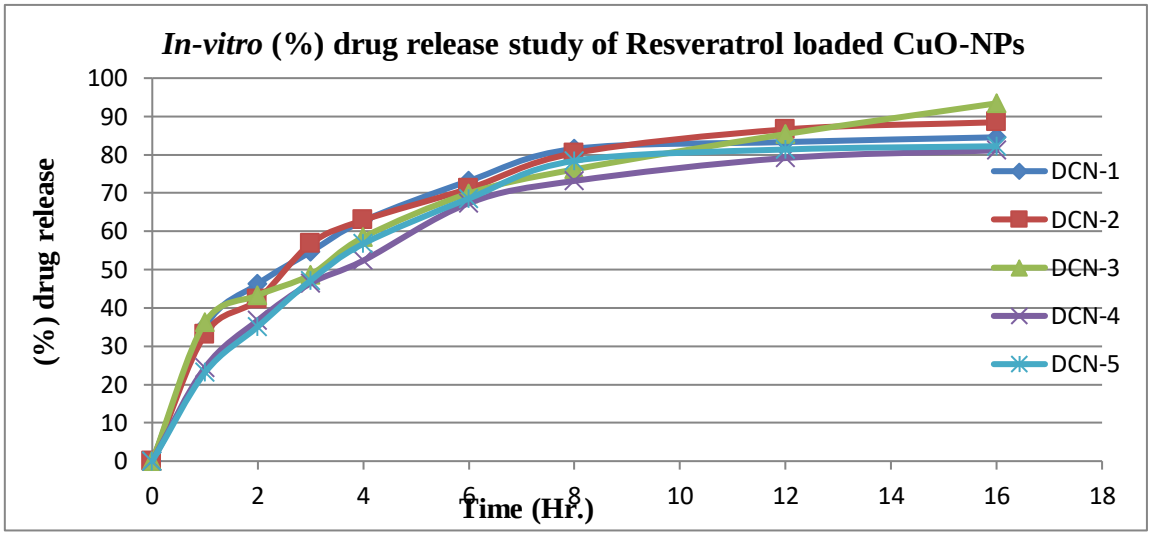

Figure 2: *In-vitro* (%) drug release study of Resveratrol loaded CuO-NPs

Kinetic Modeling of Drug Release from CuO-NPs of Resveratrol:

Comparative study of kinetic models for DCN-3 was suggested that the formulation follows the Peppas-Korsemeyer model. It suggests that the drug release mechanism is governed by diffusion-controlled kinetics, possibly with some polymer relaxation or erosion involved.

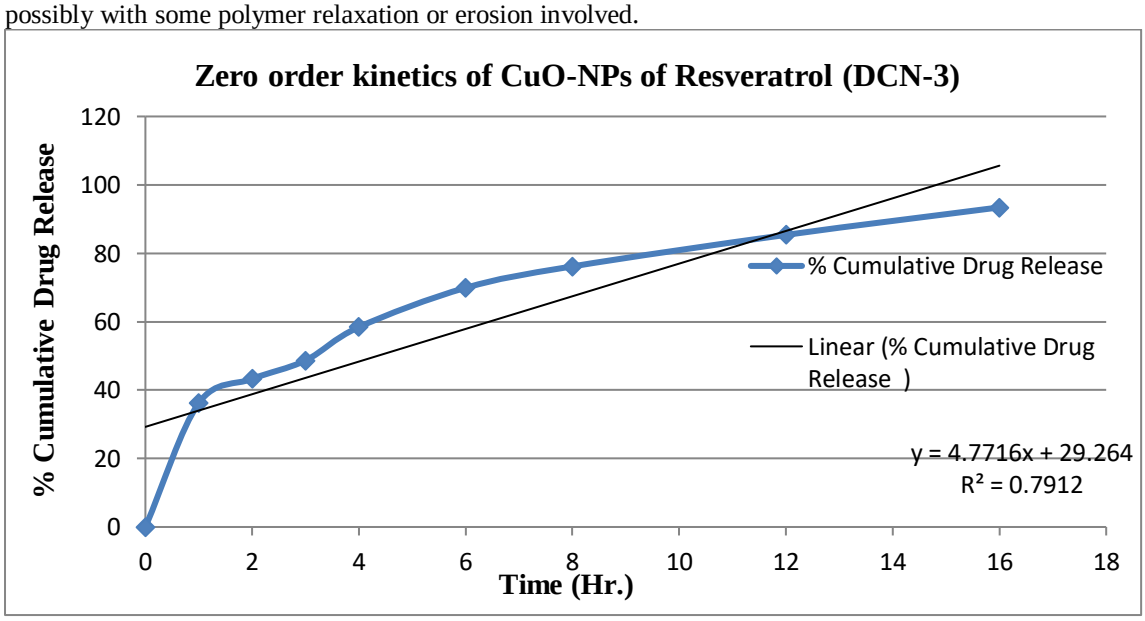

Figure 3: Zero order kinetics of CuO-NPs of Resveratrol (DCN-3)

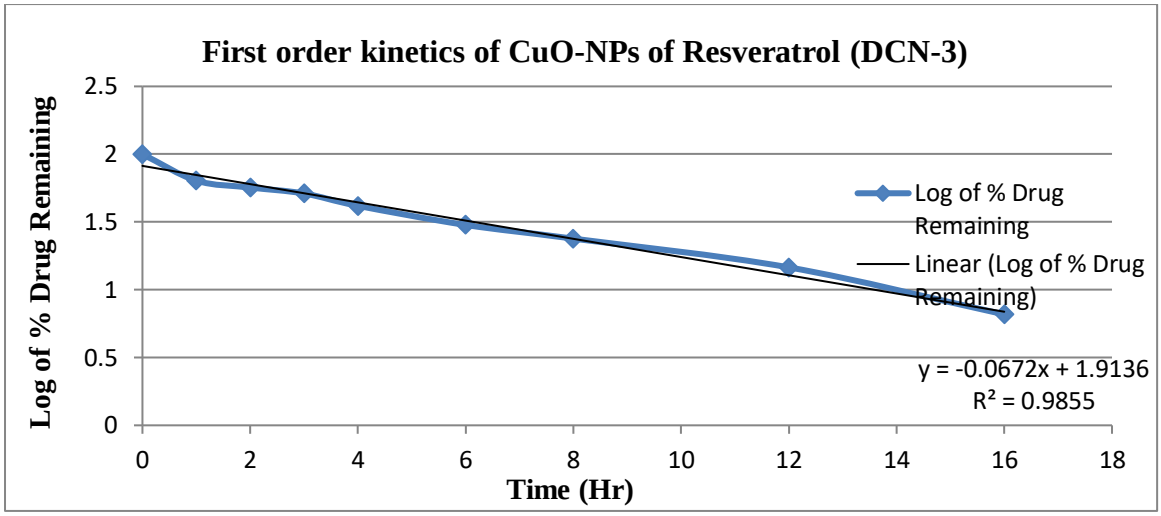

Figure 4: First order kinetics of CuO-NPs of Resveratrol (DCN-3)

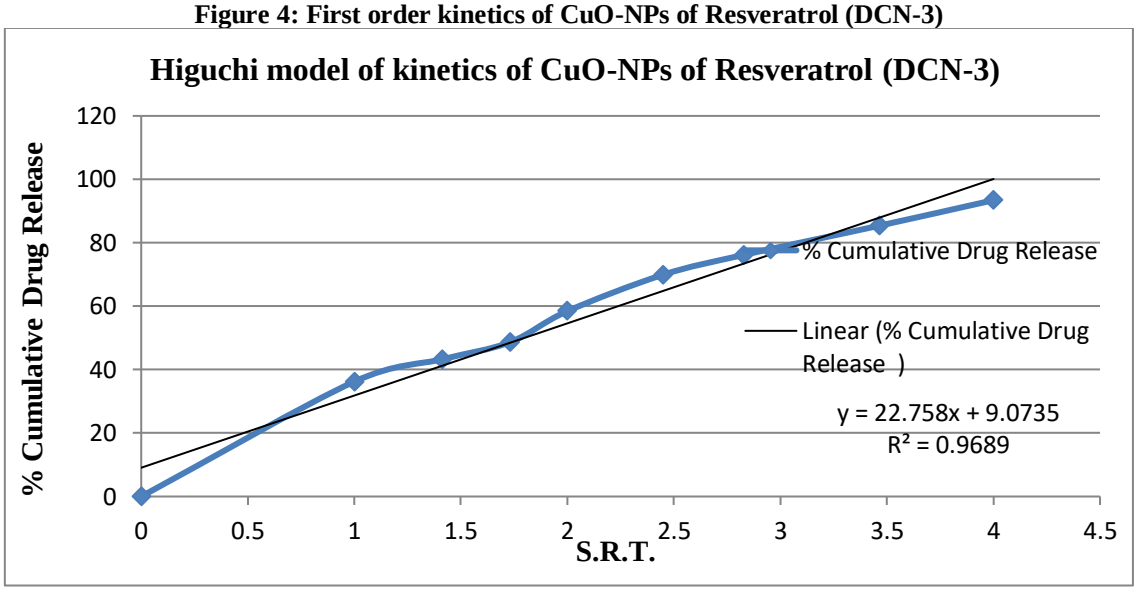

Figure 5: Higuchi model of kinetics of CuO-NPs of Resveratrol (DCN-3)

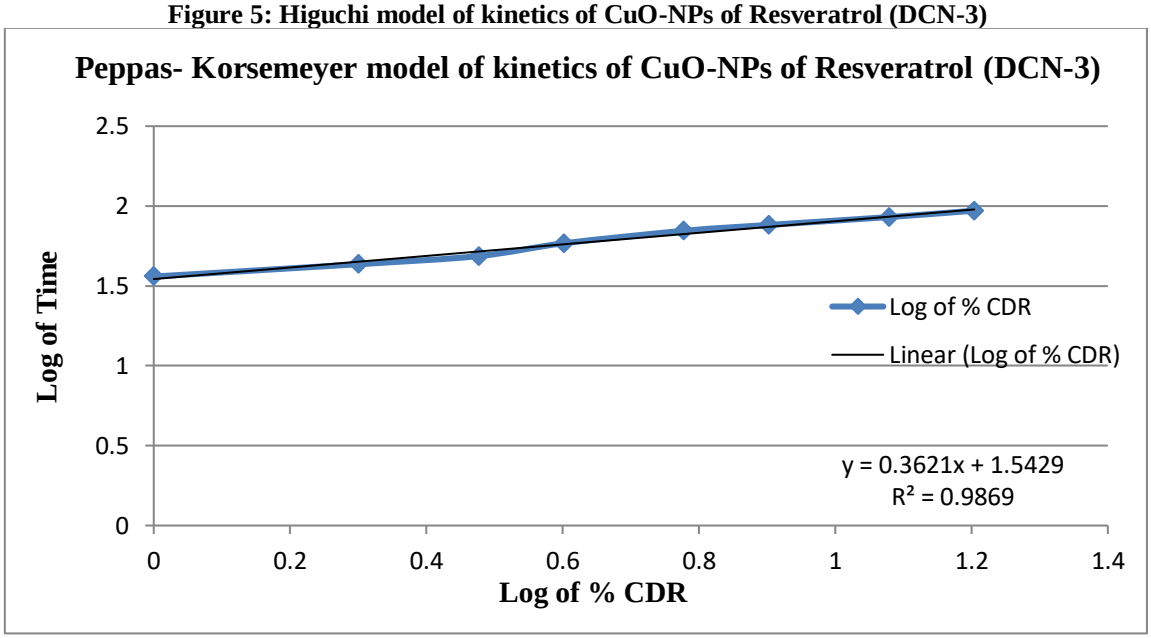

Figure 6: Peppas- Korsemeyer model of kinetics of CuO-NPs of Resveratrol (DCN-3)

Stability Study of CuO-NPs of Resveratrol (DCN-3)

There were no major changes in appearance, Drug entrapment and *in-vitro* drug release.

Table No. 4: Accelerated Stability Studies of CuO-NPs (DCN-3)

Testing parameters	Initial Readings	Room Temp.	40°C ± 2°C / 75% RH ± 5%
Particle Size (nm)	90 ± 09	91 ± 16	90 ± 13
PDI (mean)	0.198 ± 0.01	0.184 ± 0.03	0.172 ± 0.02
Zeta Potential (mV)	-3.14 ± 0.11	-3.26 ± 0.11	-3.43 ± 0.11
Entrapment Efficiency (%)	48.28	48.13	48.01
Drug Release (%)	93.42	92.83	93.26

CONCLUSION:

The present study successfully synthesized and characterized Resveratrol-loaded copper oxide nanoparticles (CuO-NPs). Resveratrol exhibited favorable physicochemical properties, including moderate lipophilicity (Log P = 8.875), solubility in relevant biological media, and a UV absorption maximum at 304 nm. Compatibility with selected excipients enabled the formulation of five nanoparticle variants (DCN-1 to DCN-5), with DCN-3 emerging as the optimized formulation. These results highlight the potential of CuO-NPs as a nanocarrier system for Resveratrol, offering controlled release and improved bioavailability, which may enhance its therapeutic efficacy in anticancer applications.

CONFLICT OF INTEREST

There are no Conflicts of interest.

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