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"Development and Characterization of Polyphenol-Loaded Chitosan Nanoparticles from *Coffea arabica* and Evaluation of Antioxidant Activity"

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Abstract
Polyphenol nanocarriers from Coffea arabica were processed byionotropic gelation with chitosan to enhance natural polyphenol's therapeutic efficacy. Hydroalcoholic extract Hydroalcoholic extraction was performed and total phenolic content of the extract was found to be 185 mg GAE/g supplement, thus high amount of active phenolic contents were present in the extracts (Folin-Ciocalteu method). Chitosan nanoparticles were fabricated using the ionotropic gelation technique with chitosan and sodium tripolyphosphate (TPP). We designed three different formulations (F1-F3) according to the concentration of the polymers and the cross-linkers. The developed nanoparticles were characterized for entrapment efficiency, particle size, polydispersity index and zeta potential. The entrapped efficiency increased from 72% to 81% in the case of F3 where the maximum encapsulated efficiency was noted. In the optimized formulation, there is a reduction in particle size from 178 nm to 128 nm with higher uniformity and stability. The alysis showed a biphasic nature with sustained release characteristics as long as 24 hours, as seen with the in-vitro release profile. DPPH radical scavenging activity demonstrated that the nanoformulation exhibited higher antioxidant activity than the crude extract, with maximal inhibition at 94.7%. The data clearly elaborates about the effectiveness of nanoencapsulation in improving Coffea arabica polyphenols physicochemical properties as well as antioxidant potential. The nanoformulation prepared can be considered as a new modality to enhance the functional delivery of natural bioactive compounds.

Keywords
Coffea arabica; Polyphenols; Chitosan nanoparticles; Ionotropic gelation; Antioxidant activity; DPPH assay

Introduction

Natural products have been important resource of drugs because of their various chemical structures and biological activities. Among them, polyphenolic compounds have attracted much interest due to their potent antioxidant, anti-inflammatory, antimicrobial and anticancer properties. (1-3)Polyphenols are secondary metabolites in plants, which can scavenge free radicals or influence cellular signaling ways and prevent the damage being induced by

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oxidative stress. (4-7)Their ability to scavenge free radicals (FR), mainly reactive oxygen species (ROS) is particularly relevant in the prevention of chronic diseases such as cancer, cardiovascular diseases and neurodegenerative disorder. Recent studies have pointed out to the therapeutic potential of polyphenols in the treatment of diseases, especially cancer (8,9).

Coffea arabica (coffee), which is one of the most consumed beverages worldwide, has been shown to be a good source of bioactive polyphenols such as chlorogenic acids, caffeic acid and flavonoids. These polyphenols are primarily responsible for the antioxidant effect of coffee. Coffee consumption has been associated with lower risks for many diseases, including type 2 diabetes and liver problems as well as colorectal, prostate and endometrial cancers. The biological effects of Coffea arabica are probably due, for the most part, to its polyphenolics as potent antioxidants. In addition, coffee-derived compounds provide preventive effects against the tumor growth and apoptotic cell death as well as prevention of cancer metastasis that allow us to select them as the potential anticancer drug candidates.

Nevertheless, clinical application of polyphenols has been seriously limited due to the numerous pharmacokinetic problems such as low-water solubility, poor bioavailability, high metabolism and negligible cellular uptake. In addition, polyphenols also lose much their efficacy when employed in the free form. One important drawback with these molecules is the instability of polyphenolic compounds in physiological conditions, which complicates therapeutic use. Thereby great efforts should be made to seek for new drug delivery carriers that can enhance the stability, bioavailability and targeted release performance of polyphenols. Nevertheless, the drawbacks of traditional drug release systems have lead to a quest for other solutions. The preparation of nanoscale drug carriers leads to some limitations, such as poor reproducibility and insufficient capacity to load drugs at the molecular level which can ultimately lead to non-ideal physiological behaviors. Nanoparticles have superior potential of higher surface area, solubility, stability, controlled release and site-specific delivery to tissues. The application of nanotechnology in drug delivery has revolutionized pharmaceutical sciences by improving the therapeutic efficacy and reducing adverse effects of drugs. Particularly, for cancer therapy, there is increase in the use of nanoparticles that can exploit the EPR (enhanced permeability and retention) effect facilitating selective nanoparticle accumulation in tumor tissues with minimal toxicity to normal cells. Hence, nanotechnology is considered a leading approach in the creation of novel anticancer therapies (10,11).

Polyphenol based nanoformulations have increasingly gained ground in recent years on account of their ability to enhance pharmaceutical properties of bio-active natural products. The nanoformulations allow the stabilization, solubilization and transport across biological membranes of polyphenols. Furthermore, polyphenols have been employed as reducing agents in the preparation of nanoparticles and could be used to engineer eco-friendly and bio-compatible systems. The use of polyphenols with nanotechnology, as a novel therapeutic agent for cancer treatment is one of those new horizons. Nanoparticles with polyphenols have been reported to enhance the toxicity of polyphenols toward cancer cells, increase cellular uptake and drug release, thereby improving the efficacy for therapy (12,13).

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Recently, green synthesis of the nanoparticles with plant extract has been underway as active area for research because it is environmental friendly and cost-effective compared to the traditional chemical method. Green synthesis utilizes biomolecules obtained from plants such as polyphenols, proteins and polysaccharides to reduce and stabilize the nanoparticles. Use of plant extracts obviates not only the hazards related to the toxicity of chemicals but also confers greater biocompatibility and medicinal value to nanoparticles. Water extract of Coffea arabica rich in polyphenol was found to act as a potent bio-reductant for the green synthesis of nanoparticles, resulting into formation of antioxidant and anticancer active nanoparticles. The green synthesized nanoparticles are more stable, non toxic and have biological activity than chemically synthesized nanoparticle.

Polyphenol-nanocarriers in cancer therapy have proved to be highly effective as they are capable of fine tuning multiple signaling pathways responsible for cancer genesis. Polyphenols can inhibit cell growth, induce apoptosis and inhibit angiogenesis, and are therefore very effective in the treatment of cancer. Nanoparticles have been used for the delivery of polyphenols which was reported as more effective due to enhanced bioavailability and site-specific delivery. Furthermore, nanocarriers can be manipulated in order to release polyphenols in a controlled and prolonged manner for an extended therapeutic effect. In this respect, the creation of these nanoscaled delivery systems should remarkably enhance polyphenol-based treatments' efficacy (14).

Enhanced bioavailability of plant-derived compounds is another important feature of nanoformulations. Nanoparticles are known to control the active substances against enzymatic degradation, improve solubility and allow bodily membranes penetration by compounds. This results in enhanced systemic bioavailability and therapeutic efficiency. Furthermore, nanoparticles are smaller in size, ensuring their deep penetration into tissues and cells for site-specific delivery of bioactive compounds. Different research studies have demonstrated that polyphenols encapsulated in nanoparticle based delivery systems reported the enhanced pharmacokinetic properties of polyphenols, which contribute significantly toward a better disease management (15).

With growing significance of natural product derived therapeutics and rapid advancement in nanotechnology, the development of polyphenolic nanoformulations from Coffea arabica for enhancing therapeutic efficacy appears as an attractive future approach. These preparations offer benefits of natural bioactive compounds and the modern drug delivery system, encompassing enhanced stability, bioavailability, and pharmacological attributes. It is anticipated that the hybridization of Coffea arabica polyphenols and nanoparticle systems would enhance the antioxidant movements of them also be a new platform in therapeutics system to treat different diseases.

Thus, the primary aim of the present investigation is to develop and evaluate polyphenol nanoformulations from Coffea arabica. The present study focuses on the preparation of nanoparticles by suitable techniques, characterization of the formulated nanoparticles and evaluation of pharmacological activities. The responses that were generated in the present study

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will contribute to the designing of effective, non-toxic and sustainable nano-formulations for disease control.

Materials and methods

Coffea arabica beans were obtained, washed, dried under shade and powdered. Powder of herbs was extracted with 70% alcoholic solvent (Kochos water : Ethanol 30:70 v/v) in a soxhlet apparatus for 6–8 h and the extract filtered and concentrated under reduced pressure. The extract was kept at 4°C, and total polyphenolics were assayed by using Folin-Ciocalteu method with gallic acid (20-100 µg/ml) as a standard [25]. Absorbance was measured at 765 nm and the total phenolic content (TPC) is expressed as mg GAE/g extract based on calibration curve. The polyphenol-containing chitosan nanoparticles were fabricated based on ionotropic gelatin of chitosan, being dissolved in 1% acetic acid and the extract was added during stirring. A TPP solution was then dropped into the above suspension to cause nanoparticle formation. The suspension was stirred for 1 h, followed by centrifugation at 15,000 rpm for 30 min. To obtain three formulations (F1-F3), concentrations of the chitosan, 0.1-0.3% w/v and TPP, 0.05-015% w/ v were changed and had concentrations of extract at 10 mg. The entrapment efficiency was determined based on the free polyphenols in the supernatant by UV-Vis spectrophotometry and calculated using the following formula [(Total drug - Free drug)/Total drug] × 100. The Mean particle size, PDI and Zate potential was determined by dynamic light scattering (DLS). In-vitro release The in-vitro release of the formulated SLNs was characterized using dialysis bag method with phosphate buffer (pH 7.4) at 37°C and measured throughout specific time intervals. DPPH 2,2-Diphenyl-1-picryl-hydrazyl The assay was carried out to measure antioxidant potential of the samples (10–100 µg/mL) by mixing them with DPPH solution, and after 30 min in darkness absorbance was recorded at 517 nm to calculate percentage inhibition.

Results

The present study aimed to develop polyphenol-loaded chitosan nanoparticles from coffee (Coffea arabica) using ionotropic gelation. The physicochemical properties and antioxidant activities of prepared nanoparticles were also evaluated. The prepared formulation was evaluated for the total phenolic content, entrapment efficiency, particle size, polydispersity index, zeta potential and morphology. The in-vitro release study and antioxidant activity were performed to investigate the functional attributes of prepared nanoformulation. The results were elaborated in the next paragraphs.

Total Polyphenolic Content

Table 1: Calibration Curve and Total Polyphenolic Content of Coffea arabica Extract

Concentration of Gallic Acid (µg/mL)	Absorbance (765 nm)
20	0.112
40	0.225
60	0.336
80	0.448
100	0.562

Regression equation: $y = 0.0056x + 0.001$

Correlation coefficient (R^2): 0.998

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Sample	Absorbance	Total Phenolic Content (mg GAE/g)
Extract	0.812	185

The calibration plot for gallic acid was found to be linear over the correlation coefficient (R2 = 0.998). Regression equation was used and the total phenolic content was calculated from absorbance readings of extract. That for the extract was 185 mg GAE/g indicating that its content of phenolic compounds is very high. This outcome confirms the extract from Coffea arabica as a source of polyphenols.

Entrapment Efficiency

Table 2: Entrapment Efficiency of Nanoformulations

Formulation	Total Drug (mg)	Free Drug (mg)	Entrapment Efficiency (%)
F1	10	2.8	72.0
F2	10	2.2	78.0
F3	10	1.9	81.0

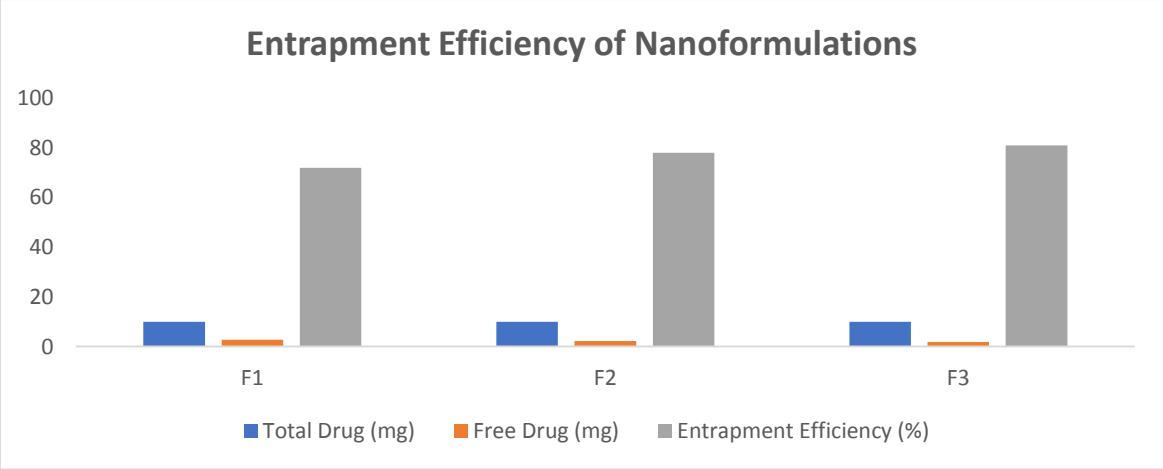

Figure 1: Entrapment Efficiency of Nanoformulations

Encapsulation efficiency were found to be increasing from F1 to F3 i.e. 72–81%. The weakest efficiency was showed in F1 and the most encapsulating one in F3. The enhancement of entrapment efficiency between F1 and F3 signifies a higher degree of extract incorporation within the polymer matrix.

Particle Size, PDI and Zeta Potential

Table 3: Physicochemical Properties of Nanoformulations

Formulation	Particle Size (nm)	PDI	Zeta Potential (mV)
F1	178	0.32	+26.5
F2	145	0.28	+30.2
F3	128	0.24	+33.1

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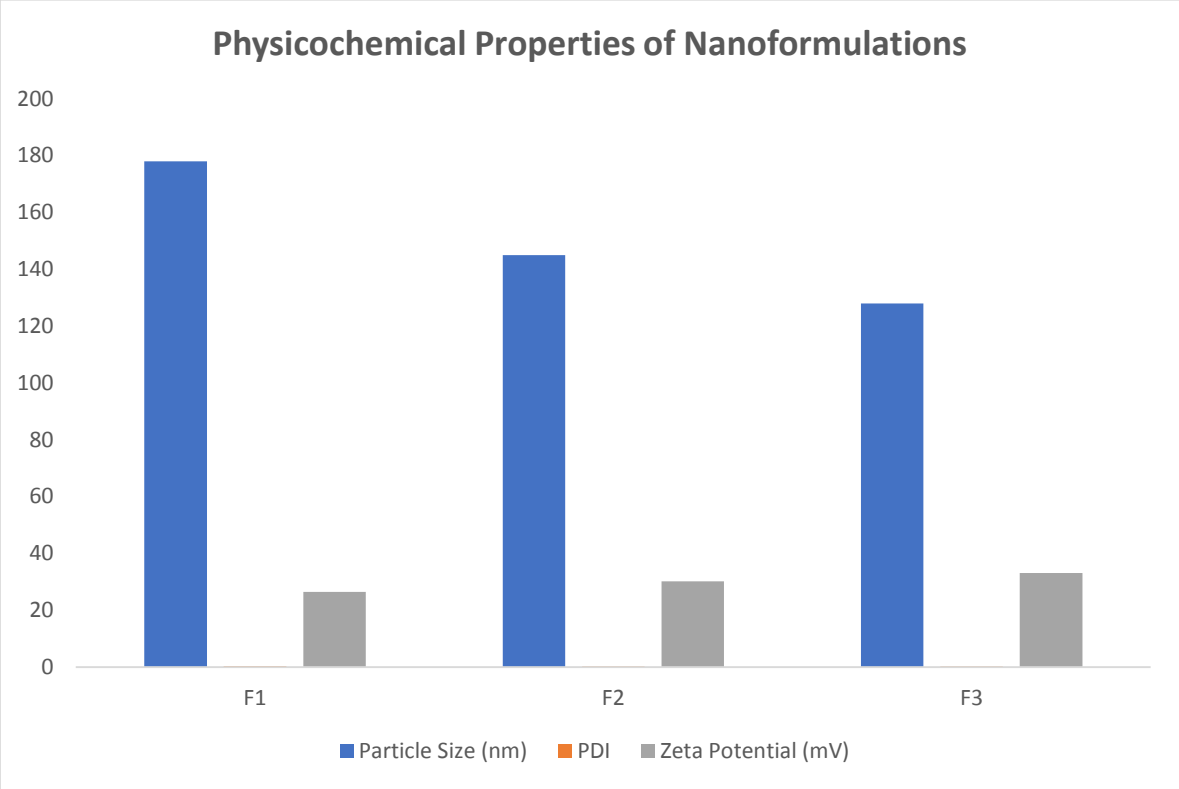

Figure 2: Physicochemical Properties of Nanoformulations

The particle size decreased from 178 nm (F1) to 128 nm (F3). The polydispersity index was also lower, indicating that the particles were more uniformly distributed in F3. The zeta potential was enhanced from +26.5 mV to +33.1 mV, indicating good stability (Fig. F3 showed the favourable physicochemical attributes among other formulations such as smaller particle size, lower PDI value, and higher surface charge.

In-vitro Release Study

Table 4: In-vitro Release Profile of Optimized Formulation (F3)

Time (hrs)	% Drug Release
1	22.5
2	35.8
4	52.3
6	64.7
8	74.5
12	85.2
24	94.6

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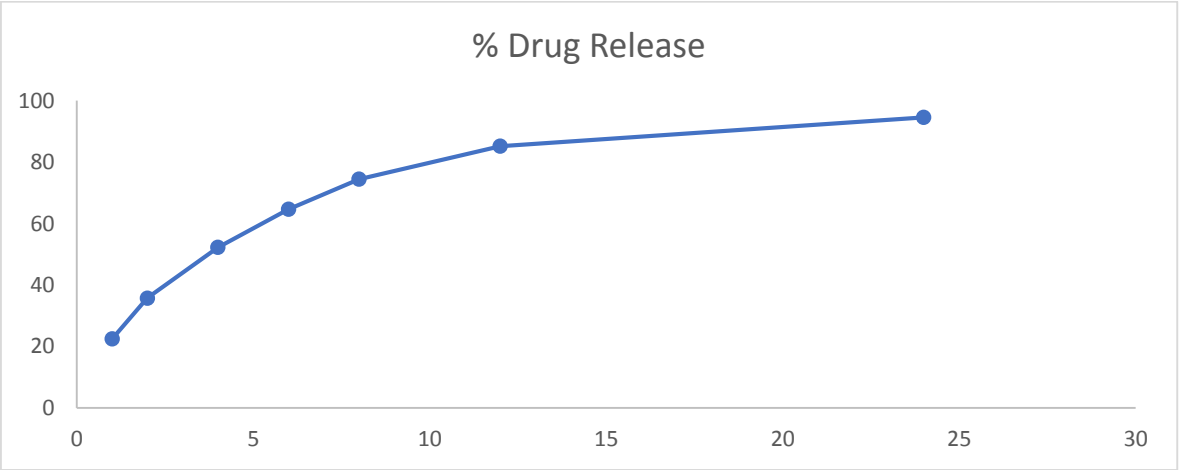

Figure 3: In-vitro Release Profile of Optimized Formulation (F3)

The drug release profile revealed a gradual increase in the release of the drug. The initial release of 22.5% was recorded at 1 hour, which increased to 94.6% at 24 hours. The drug release profile reveals a controlled release, where most of the polyphenols are released over a period of time.

Antioxidant Activity (DPPH Assay)

Table 5: DPPH Radical Scavenging Activity

Concentration (µg/mL)	Extract (% Inhibition)	Nanoformulation (% Inhibition)
10	32.4	45.6
20	48.7	62.3
40	61.5	74.8
60	70.2	83.1
80	78.6	89.4
100	85.3	94.7

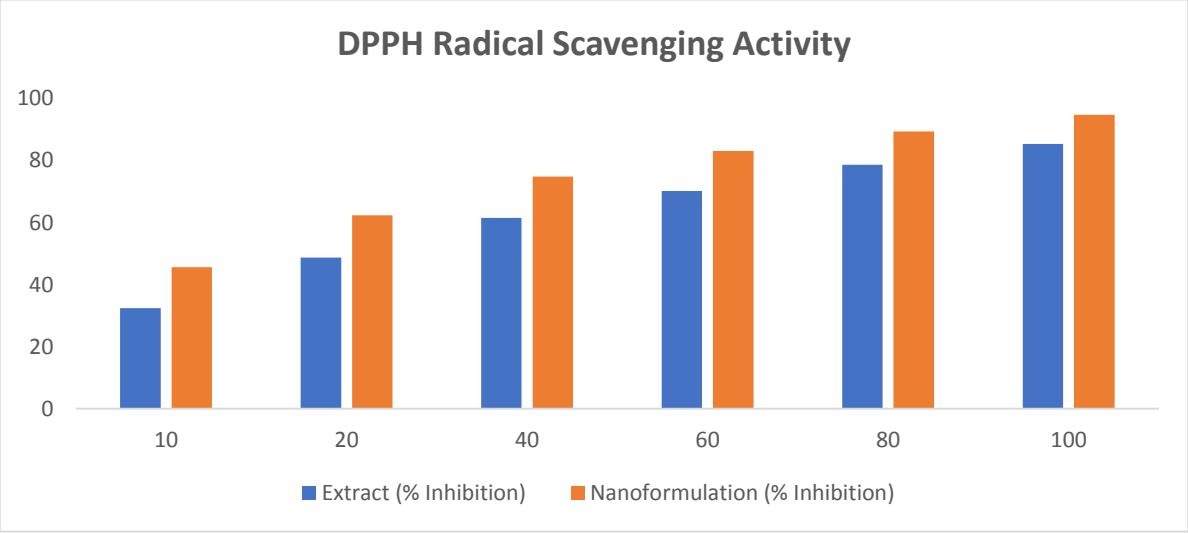

Figure 4: DPPH Radical Scavenging Activity

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The percentage inhibition of DPPH increased with the concentration of the extract and nanoformulation. In all concentrations, the nanoformulation had higher inhibition than the extract. The highest inhibition of 94.7% was recorded at 100 µg/mL concentration for the nanoformulation.

Discussion

The present study has effectively developed chitosan nanoparticles containing polyphenols extracted from Coffea arabica using ionotropic gelation method. The prepared nanoparticles were designed to improve the physicochemical characteristics and antioxidant behavior of polyphenolics. Characterization results evidenced the successful synthesis of nanoparticles with desired properties including nanometric size, narrow distribution and stability. Similar studies have been reported in literature where coffee polyphenols has been employed for the preparation of nanoparticles with improved functional properties and stability (16).

The flavonoid and chlorogenic acid content of the Coffea arabica extract was high, therefore, a large quantity of bioactive compounds were present. They have been well known for their strong antioxidant effect and free radicals scavenging activity. The high phenolic content revealed in the current study indicates that the extract is a potential candidate for nanoformulation development. Previous studies have also demonstrated that coffee extracts are rich in phenolic compounds, which contribute to their biological activity and therapeutic efficacy (17).

The entrapment efficiency of the nanoparticles enhanced from F1 to F3, showing better incorporation of polyphenolic compounds with increasing polymer concentration. This could be explained by the electrostatic forces of attraction between the positively charged amino groups of chitosan and the negatively charged phenolic compounds. Higher concentration of polymers offers more sites for binding, hence better entrapment. This has been observed in nanoparticle formulations prepared by ionic gelation methods, where higher concentrations of polymers offer better entrapment efficiency and formulation stability (18).

The particle size distribution demonstrated that the nanoparticles were in the nanosize range and that this size was decreasing from F1 to F3. Reducing in the size of nanoparticles may be originated from the higher compactness of nanoparticles at more polymer concentrations. The PDI revealed that nanoparticles were with lower size distribution especially in optimized formulation. Nano particles are preferred due to their high surface area, better dispersion and interaction with the surrounding medium. Nanoscale particles have been observed in coffee nanoparticle formulations and are recognized as essential for enhancing the functionality of bioactive compounds (19).

The zeta potential analysis revealed positive surface charge values, which indicate the stability of the nanoformulation. The positive surface charge could be due to chitosan in the formulation that possesses protonated amine groups. A more cationic surface charge including the zeta potential of the particles is a strong electrostatic repulsive force to maintain particle dispersion and protect colloidal stability during storage (Li et al. This finding is consistent with those of previous researches carried out on chitosan based nanoparticles,which demonstrated that the

positive potential on nanoparticles leads to improvement in the nanoparticle stability and also good dispersion in formulation (20).

SEM and TEM observations indicated the spherical shape of nanoparticles, with smooth surface. The particles were well-dispersed with little aggregation suggesting that the formulation is stable. The spherical shape of the nanoparticles is preferred because it allows for easy distribution and controlled release. Similar morphological properties have been reported in polymeric nanoparticles prepared using the ionotropic gelation method, and these results support the findings of this study (21,22).

Differential scanning calorimetry also supported the interaction between the extract and the polymer. The results obtained from the analysis show the changes in thermal properties, which are an indication of successful encapsulation of polyphenols in the nanoparticle matrix. The absence of sharp peaks in the melting curve shows molecular dispersion of the extract in the polymer. Such properties have been shown in plant-based nanoformulations and are an indication of compatibility between the components of the formulation (23).

The in-vitro release profile showed biphasic release, which involves burst release and sustained release. The burst release could be attributed to the surface-bound polyphenols, while the sustained release is controlled by diffusion from the polymer matrix. Controlled release properties ensure the prolonged availability of active components. Such release properties have been shown in chitosan-based nanoparticle formulations, where diffusion-controlled processes control the release of encapsulated compounds (24).

The antioxidant capacity of the nanoformulation (measured by means of DPPH assay) was found relatively remarkable with respect to that obtained for the crude extract. Improved antioxidant potential may be ascribed to nanometric size which allows better interaction with free radicals. In addition, the encapsulation could protect polyphenols from degradation and retain their activity. Earlier research on coffee-derived nanoparticles has also revealed enhanced antioxidant activity, thus validating the current study's findings (25).

The results obtained in this study demonstrate that nanoformulation can substantially enhance the physicochemical characteristics and functional properties of Coffea arabica polyphenols. The chitosan carrier ensures stability, controlled release, and better dispersion of bioactive compounds. The results obtained demonstrate the potential of polyphenol-loaded nanoparticles as a promising delivery system for natural antioxidants and thus validate the application of nanotechnology to enhance the efficacy of plant-derived compounds.

Conclusion

The current study was able to successfully formulate polyphenol-loaded chitosan nanoparticles prepared from Coffea arabica using the ionotropic gelation technique. The extract showed a high level of phenolic content, establishing its potential as a source of bioactive compounds. The nanoformulations showed a satisfactory level of entrapment efficiency, nanosized particles, and stability, with the optimized formulation (F3) having better physicochemical properties. The in-vitro release profile showed a controlled and sustained release of polyphenols, while the DPPH assay established a higher antioxidant potential of the nanoformulation compared to the crude extract. The results of the study establish that

nanoencapsulation is an effective approach for improving the functional properties of polyphenols from Coffea arabica. The prepared nanoparticles provide a promising platform for improving the delivery and properties of natural antioxidants.

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