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Original Article

Synthesis and *in vitro* Evaluation of Zinc Ferrite Nanospheres for Sustained Carvedilol Drug Delivery

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ABSTRACT

Background: Magnetic nanoparticles has significant applications, in MRI contrast enhancement, tissue regeneration, cancer therapy, controlled drug delivery etc. The nanoparticles can be tailored to possess specific attributes suitable for distinct biological applications, as a potential drug carriers for sustained drug release. **Materials and Methods:** The present study focused on synthesizing and utilizing magnetic mesoporous Zn-Ferrite Nanospheres (Zn-Fe NSs) as carriers for controlled drug release systems. Zn-ferrite nanospheres were synthesized by encapsulating the drug carvedilol, by facile solvothermal approach. Thermo Gravimetric Analysis (TGA), Fourier Transforms Infrared Spectroscopy (FT-IR), Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), Atomic Absorption Spectroscopy, and X-ray Diffraction (XRD) techniques were used to characterize the Zn-Ferrite nanospheres. **Results:** The average particle size of unloaded and drug-loaded Zn-Ferrite nanospheres was 262.8 nm and 247.6 nm, with polydispersity values of 0.19 and 0.2 Respectively. *In vitro* drug release studies shown 95.47% cumulative drug release from carvedilol-loaded Zn-Fe NSs after 12 hr at a pH of 7.4. The kinetic studies revealed that the Korsmeyer Peppas model provided the best fit, indicating quasi-Fickian diffusion with a release exponent value of 0.15. **Conclusion:** The investigation of carvedilol-loaded Zn-Fe NSs revealed a sustained drug release pattern, which is considered crucial for the treatment of cardiovascular diseases, hypertension, cardiopulmonary arrest, and hypertension conditions.

Keywords: Drug delivery, Magnetic nanoparticles, Nanocarrier, Sustained drug release.

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INTRODUCTION

Nanotechnology is rapidly advancing within the pharmaceutical industry, prominently utilised for nanomedicines and drug delivery systems. Nanoparticles play a pivotal role by enhancing efficacy and mitigating adverse drug reactions.[1,2] These nanoparticles exhibit promising applications in various domains, including *in vitro* drug release systems, *in vitro* diagnostics, medical implants, therapeutical techniques, nanocarrier tracking, tissue engineering, and more.[2-4] Current nanotechnology offers the potential for enhancing formerly approved drugs and therapeutic products, presenting opportunities for improvement and innovation.[5] Nano-medicinal research is blooming but drug delivery systems with nanoparticles have had more attention among researchers over the past decade.[6] An increase of 75% revenue with the incorporation of this technology infused into pre-approved Active Pharmaceutical Composition.[7] Nanoparticles measuring between 10 and 1000 nm in diameter have been effectively combined with Antigen-Presenting Cells (APCs) through methods like entrapment, encapsulation or dissolution. The amalgamation of nanoparticles and Antigen-Presenting Cells (APCs) has demonstrated exceptional effectiveness within drug delivery systems.[8,9] The nanoparticles have been synthesised in different forms, including CNTs (carbon nanotubes), nano-magnetic particles, nano-emulsions and dendrimers.[10-14] Nano-magnetic particles are suited better for the drug delivery system as they could be tailored as per the biological applications. The magnetic nanoparticles could also be utilised as drug carriers to the areas of the body where conventional drug delivery systems would not be effective. The magnetic properties of the nanoparticles utilised as drug carriers have to be super paramagnetic unblocked with minimal blocking temperature and coercivity.[15] Henceforth, the nanomagnetic particles must be customized efficiently as per their bio-medicinal applications.

The synthesis of transition metal ferrite nanostructures has attracted a lot of interest recently with the molecular formula MFe_2O_4 (M-represents the ferrite doped with various metals like Zn, Cu, Ni, Mn, Co, etc.,). This is due to both their profound impact on the fundamental understanding of physical processes coupled with their proposed significance and endless application in various fields.[16] Zn-Ferrite has fascinating magnetic,

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electromagnetic and thermodynamic properties.[17] With Zn^{2+} integrated at the tetrahedral lattice A site and Fe^{3+} at the octahedral lattice B site of the AB_2O_4 spinel lattice, Zn-Ferrite possesses a typical spinel structure. The interaction between metallic ions holding particular spots in relation to the oxygen ions inside the oxide's crystal structure gives rise to the magnetic property.[18] Zn-ferrite nanoparticles have emerged as a new generation of the matrix for controlled drug deliveries in nanomedicine because of their biocompatibility, high colloidal adherence and ability to be customized with biological molecules.[19] By adjusting its particle size and synthesis circumstances, the $ZnFe_2O_4$ compound's magnetic behaviour can be tuned.[20] The surface coating of MNPs is crucial for the practical usage of magnetic particles in clinical applications. Long-chain organic ligands or inorganic/organic polymers may be used as the coating, and they may be added either during the synthesis (*in situ* coating) or after the synthesis (post-synthetic coating). The performance of Magnetic Nanoparticles (MNPs) in biomedical applications depends on the coating material that has been employed as well as the materials attached to the magnetic core because surface modification of MNPs has the potential to significantly alter the magnetic properties.[21-23]

Various preparation techniques have been reported for the synthesis of $ZnFe_2O_4$ nanostructures namely solvothermal,[24] sol-gel method and emulsion-templated synthesis.[25] Solvo-thermal also named hydrothermal methods are majorly used for the synthesis of nanoparticles which is due to the simple synthesis conditions, and control of the size and morphology of nanostructure materials by using different solvents.[26,27]

Nanocrystalline spinel Zn-Ferrite has potential applications in biomedicine such as drug delivery, hyperthermia treatments, anticancer treatments, and Magnetic Resonance Imaging (MRI) contrast enhancement.[28] Hitherto, numerous works have been outlined on the magnetic property and application of $ZnFe_2O_4$ magnetic nanoparticles. Cui and his team prepared Zn-Ferrite particles coated with chitosan and loaded with lidocaine drug. A duo-responsive system was developed and the anaesthetic drug delivery system efficiency was studied.[29] Sun *et al.*, had worked on three shaped Mn-Zn ferrite (Mn 0.63 Zn0.37 $Fe2O_4$) MNPs which were used in cancer theranostic agents. PEG-coated nanomagnetic particles have efficiently helped in tumour cell killing. The diagnosis and tumour killing had been achieved simultaneously.[30] Mabrouk with his team had worked on zinc nanoparticles (NPs) coated with chitosan and loaded with ciprofloxacin drug. The cell viability, proliferation and biocompatibility increased with these NPs.[31]

Carvedilol is a medication commonly employed for treating cardiovascular diseases, hypertension, and cardiopulmonary arrest. It belongs to BCS (Biopharmaceutics Classification System) Class II drugs, characterized by their poor solubility in water. This classification is denoted by its partition coefficient (log P) value, which for carvedilol is 4.115. A log P value greater than 1 indicates lipophilicity, which typically corresponds to low water solubility. Consequently, the bioavailability of carvedilol falls within the range of 25-35%, which signifies the limited amount of the drug that reaches the bloodstream unchanged after oral administration.

To address this challenge and enhance the therapeutic efficacy of carvedilol, a controlled drug release approach could be adopted. This technique involves the strategic design of the drug formulation to control its release rate and thereby optimize its absorption and distribution in the body. By modulating the release kinetics, the dissolved concentration of the drug can be maintained within the therapeutic range for an extended period, enhancing both its efficacy and safety profile.

The current work reports the synthesis and application of mesoporous Zn-Ferrite nanospheres as carriers for controlled drug release formulations. A model anti-hypertensive drug carvedilol loaded magnetic Zn-Ferrite nanospheres have been synthesised by facile solvothermal method. Drug-loaded $ZnFe_2O_4$ particles were systematically characterized by XRD, TGA-DSC, SEM, TEM, AAS and FT-IR. *In vitro*, the release of drugs from carvedilol-loaded Zn-Ferrite and their release kinetic studies were carried out. Zn-Ferrite nanospheres filled capsule formulation has been prepared and the capsules were also evaluated. The significance of this work is to evaluate the synthesised drug-loaded nanoparticles and to check whether the capsules met the standards and could be introduced into the commercial market. Compared to other ferrites like Fe_3O_4 and $MnFe_2O_4$, Zn-Ferrite ($ZnFe_2O_4$) has attracted a lot of interest as a drug carrier because of its improved stability, reduced toxicity, and increased biocompatibility. Zn-Ferrite is a perfect choice for drug delivery applications because of its spinel structure, which enables greater surface modification. Zn-Ferrite nanoparticles are a better option than conventional ferrite nanoparticles since they have been shown to have greater dispersion stability and better control over drug release kinetics.

MATERIALS AND METHODS

Materials, Chemicals and Reagents

Carvedilol drug and gelatin empty capsules were procured from M/s. Shazun Pharmaceuticals, Chennai, India and M/s. Kniss Laboratories Chennai, India. The other chemicals namely $ZnCl_2$ (SD Fine Chemical Ltd., Mumbai, India), Sodium acetate (Nualigens, Mumbai, India), Ethylene glycol (Merck Specialities Pvt. Ltd., Mumbai, India), $FeCl_3.6H_2O$ (Loba Chemie, Mumbai, India) and D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS 1000, Sigma-Aldrich Co., Bangalore, India), N, N'-Dimethyl formamide (DMF, SISCO Research Lab, Mumbai, India), Acetone (Himedia laboratories Pvt. Ltd., Mumbai, India), Ethanol (Hayman Ltd., UK) were used. All the chemicals being analytical grade were utilised for the current study without

any additional purification. All the trials were conducted using millipore water with a conductivity of 1.83 MΩ.cm. Experiments were duplicated and the average data was reported in the article.

Fabrication of $ZnFe_2O_4$ Nanospheres

The solvothermal synthetic route was chosen for the synthesis of Zinc ferrite Nanospheres (NSs). 2.7 mmol of $FeCl_3.6H_2O$ was dissolved in 80 mL ethylene glycol. 4.1 mmol of $ZnCl_2$ was mixed and homogenised. Further, 26 mmol of sodium acetate was added and the whole solution was stirred continuously for 10 min at ambient room temperature using a magnetic stirrer. After being homogenised, the solution was put into a 100 mL Teflon-lined autoclave and heated for 12 hr at 200°C. After centrifuging the mixture, ethanol was used to wash the supernatant. The final product, $ZnFe_2O_4$, was then dried in a hot air oven for 4 hr at 50°C.

Dispersion Stability Study of Polymer Functionalized Zn-Ferrite NSs

The polymers chosen were D-α-Tocopherol Polyethylene Glycol 1000 Succinate (TPGS 1000), Polyoxyethanyl-α-tocopheryl sebacate (PTS), Poly (isobutylene-co-maleic acid) sodium (PIBMS), DL-α-Tocopherol Methoxy Polyethylene Glycol Succinate (TMPGS) and Aminopropyl Triethoxy Silane (ATS). Polymer functionalized Zn-Ferrite NSs (0.1 wt. %) dispersed in 10 mL of distilled water were sonicated for 4 min at consequent two-time pulse intervals and left undisturbed overnight. The dispersion stability of polymer functionalized Zn-Ferrite NSs was analysed through the transmittance using a UV-visible spectrophotometer (λ_{Max}=242 nm).

Zn-ferrite NSs were sonicated into a suspension in 115 mL of DMF (15 mL). The solution was gradually supplemented with TPGS 1000 and was continuously stirred for 45 min at 80°C. Centrifugation was used to yield Zn-Ferrite NSs, which were washed off with DMF and dried in the open air for future use. TPGS 1000 was chosen as the best stabilizer because of its capacity to increase drug solubility, inhibit agglomeration, and improve nanoparticle dispersion. Polydispersity Index (PDI), zeta potential, and particle size were measured in a comparative research to support the choice of TPGS 1000 over alternative surfactants. Better colloidal stability was indicated by the nanoparticles stabilized with TPGS 1000, which had the lowest PDI (0.19) and a strong negative zeta potential (-22.3 mV). PVA or Tween 80-will stabilize nanoparticles, on the other hand, exhibited more aggregation and decreased drug retention.

Drug Stocking Process into Polymer Functionalized Zn-Ferrite NSs

The drug loading process was performed at 1:1 to 3:1 proportions of polymer functionalized carrier and carvedilol drug with ethanol as dispersing medium. The solution was sonicated for 10 min at consequent three-time pulse intervals. Following the sonication procedure, the products were centrifuged for 10 min at 6000 rpm with the decanted solutions being precisely dried and weighed.

The drug Encapsulation Efficiency (EE%) was calculated using the equation (1).

$$EE(\%)=\left(\frac{W_i - W_f}{W_i}\right) \quad (1)$$

where W_i represents the initial weight of carvedilol, and W_f is the unencapsulated drug recovered after centrifugation. The encapsulation efficiency was determined using UV-Vis spectrophotometry at λ_{Max}=242 *nm*, with three replicates to ensure reproducibility. The amount of carvedilol drug loaded could be measured using the equation drug load efficiency wt.%=(w_1-w_2)/w, where w_1, w_2, and w express the initial weight of carvedilol, the weight of carvedilol present in excess ethanol and weight of Zn-Ferrite NSs respectively.

Drug-Loading

Hand filling method was utilised to fill one capsule with 25 mg of carvedilol drug into pre-weighed (241.80 mg) drug-loaded Zn-Ferrite NSs with some pharmaceutical excipients namely diluents, disintegrants and preservatives.

Characterization Studies

The particle morphology of carvedilol-loaded n-Ferrite NSs was studied with quanta 200 FEG High-Resolution Scanning Electron Microscope. Energy-Dispersive X-ray Analysis (EDAX) was used to accomplish the elemental analysis. With a transmission electron microscope, particle size was calculated. Zetasizer Nano ZS (Malvern Instrument, UK) was used to measure the zeta potential of nanoparticles with a Helium-Neon laser at 633nm at a 90° angle. The common KBr pellet technique was used to record FT-IR spectra using a PERKIN ELMER (Spectrum RX1, FTIR V.200) spectrophotometer. Cu K∞ radiation was used in an X-ray diffraction technique (Philips PAN analytical, Netherlands) to examine the phase evolution of the powder sample. With TG-DSC analysis (Netzsch STA 449 F3 Jupiter Build) under N_2 conditions and a heating rate of 10°C/min from room temperature to 1200°C, the thermal stability of the compound Zinc ferrite and drug was investigated.

In vitro studies on carvedilol drug release

The *in vitro* drug release of carvedilol from carvedilol-loaded Zn-Ferrite nanospheres was studied in a continuous drug release manner at different pH of the Gastro-Intestinal Tract. The dialysis bag (cutoff 5 kDa; Himedia Q14, India) was filled with Zn-Ferrite NSs equivalent to 30 mg of the drugs, which were then dissolved in 3 mL of dissolution media. The receptor compartment filled with the dissolving medium was maintained at pH 1.2, 4.5, 6.8 and 7.4 and it was stirred continuously at 37±5°C. The dialysis

bag was dipped in this compartment. The drug samples were taken at various time intervals (up to 24 hr) and the volume of the compartment was maintained constant with a fresh dissolution medium. The release of the drug was quantified using a UV-visible spectrophotometer (λ=241 nm).

The kinetic models namely zero order, first order, Higuchi and Korsmeyer- Peppa models were utilised to analyse the kinetics of drug release. The zero-order kinetic model would deliberate whether the drug release is independent of its concentration. First-order kinetics would express the interdependence of drug release with concentration. Diffusion through Fick's law could be concluded with the Higuchi model and Korsmeyer- Peppa's model would derive a polymeric expression to study the drug release kinetics.[32]

Studies on Filled Capsule

Weight Variation Test

To study weight variation, 20 capsules were weighed all together and the test was performed as per the Indian Pharmacopoeia (I.P) official method. 20 capsules were also individually weighed, and the average weight was determined. According to I.P. Specification, the percentage deviation shouldn't be greater than 7.5% for capsules with an average weight between 80 and 250 mg.[33-36] The average weight of the capsule should not cross 250 mg. A deviation of ±10 % is acceptable.

Disintegration Test

The disintegration test was conducted in distilled water as per the official method (I.P) with tablet disintegration apparatus.[37-42]

Dissolution Studies/*In vitro* Drug Release of Carvedilol Loaded Zn-Ferrite Nanospheres (Zn-Fe NSs)

The rate of drug release in the solution is expressed by the dissolution test. In this study, the paddle method of dissolution test was used. 900 mL of 0.1 HCl was the solution taken and the paddle was rotated at 100 RPM. The drug quantitation was measured using HPLC.[43-45]

RESULTS

The polymer functionalised Zn-Ferrite NSs solution transmittance (%) was interpreted using UV-vis spectrophotometer. Among the chosen polymers, comparatively, TPGS 1000 had shown the lowest transmittance of 3.04 nm at λ_{Max}=242 nm. The crystal structure and morphology of the nanocrystalline $ZnFe_2O_4$ superstructure was investigated using TEM analysis as shown in Figure 1 and it confirms that the particles developed are of nano-scale. The particle size of 100 nm was observed and confirmed with XRD analysis too. X-ray diffraction analysis was performed on the pure drug (Carvedilol), pure carrier ($ZnFe_2O_4$) and carvedilol-loaded $ZnFe_2O_4$ carrier.

From XRD analysis the reflection planes (220), (311), (400), (422), (511), and (440) confirm ed the presence of single-phase $ZnFe_2O_4$ with a face-centered cubic structure. The interlayer space between Zn-Ferrite was found to be 7.4068 Aº . This interspace has been increased to 8.2122 Aº in the case of drug-loaded Zn-Ferrite. The increase in the interlayer spacing (d) represents that the drug has been loaded into Zn-Ferrite. The diffraction peaks of the samples match well with the standard pattern of cubic $ZnFe_2O_4$ with a spinel structure (JCPDS file no. 22-1012). Additionally, the XRD patterns displayed reflection planes (220), (311), (400), (422), (511), and (440), which supported the existence of single-phase $ZnFe_2O_4$ with a face-centred cubic structure.

The zeta potential measurement was used to assess the surface charge of the Zn Ferrite nanoparticles produced. Typically, zeta potential values exceeding +30 mV or falling below -30 mV are indicative of stable suspensions. However, the recorded zeta potential for the synthesized nanoparticles suggested potential aggregation. As attraction begins to outweigh repulsion, particles tend to aggregate. leading to changes in the zeta potential. The zeta potential value of drug-loaded Zn-ferrite was less than the zeta potential value of Zn-ferrite thereby concluding the effective drug loading.

The particle size of the samples Zn-Ferrite nanospheres selected TPGS 1000 Polymer functionalized Zn-ferrite nanospheres and drug-loaded Zn-Ferrite nanospheres were analyzed using differential light scattering. The average particle size was observed to be within the range of 240-320 nm and polydispersity of 0.19 to 1. Polydispersity is the measure to show the even distribution of the particles and if its value increases the stability also increases.

The TGA analysis was carried out for pure carrier and carrier with different amounts of drug-loaded formulations, polymer functionalized Zn-Ferrite and polymer functionalized Zn-Ferrite carrier (1:1, 1:2, 1:3, 1:4, 1:5, 2:1, 3:1). Due to the decomposition of organic compounds initial weight loss had occurred. The percentage of drug loaded to each formulation can be found from the residue obtained. It could be observed that the ratio of 1:5 was the high drug-loaded formulation. The other inferences were by decreasing the drug ratio the percentage of drug loading also decreased. The decomposition (%) of polymer functionalized Zn-Ferrite was greater than pure Zn-Ferrite which indicated that the polymer has been functionalized with the pure Zn-Ferrite carrier. The drug-loaded polymer functionalized Zn-Ferrite (1:5 ratio) was compared with pure Zn-Ferrite carrier; the former had a high percent of drug loading due to a high percent of decomposition.

Differential scanning calorimetry analysis was carried out for pure drug, pure carrier and drug-loaded Zn-Ferrite of different ratios, polymer functionalized Zn-Ferrite and polymer functionalized drug loaded Zn-Ferrite at different ratios. A peak was observed

near 117.92°C for the pure drug whereas no deflection was observed for the carrier as it is an inorganic material.

Atomic absorption spectroscopy was carried out for Zn-Ferrite, Zn-Ferrite drug loaded, TPGS 1000 Polymer functionalized Zn-Ferrite, TPGS 1000 Polymer functionalized Zn-Ferrite drug loaded, PIBMS Polymer Functionalized Zn-Ferrite and PTS Polymer Functionalized Zn-Ferrite to estimate the concentration of iron and zinc ions. The encapsulation efficiencies of Zn-Ferrite nanospheres utilizing various stabilizers (TPGS 1000, PVA, and Tween 80) were compared using a one-way ANOVA analysis. In comparison to PVA (78.2%) and Tween 80 (72.5%), TPGS 1000 offered the highest encapsulation efficiency (84.6%), according to the data, which showed a significant difference ($p<0.05$). The amphiphilic characteristic of TPGS 1000, which improves drug solubility and encourages homogeneous drug dispersion within the nanocarrier matrix, is responsible for this increased efficiency.

In vitro Continuous Release of Carvedilol from Zn-Fe Drug-Loaded Nanosphere

In vitro continuous release of carvedilol drug Zn-Fe drug-loaded nanosphere studies were performed using dialysis bags.[46] The percentage of drug release with the change in time and pH

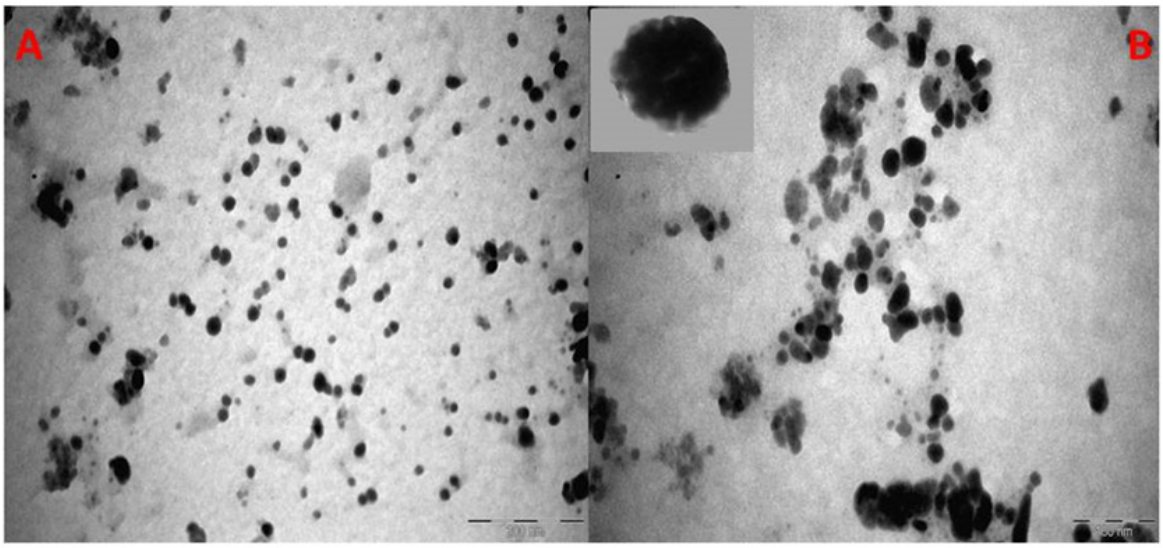

Figure 1: TEM image of Zn-Ferrite nanoparticles.

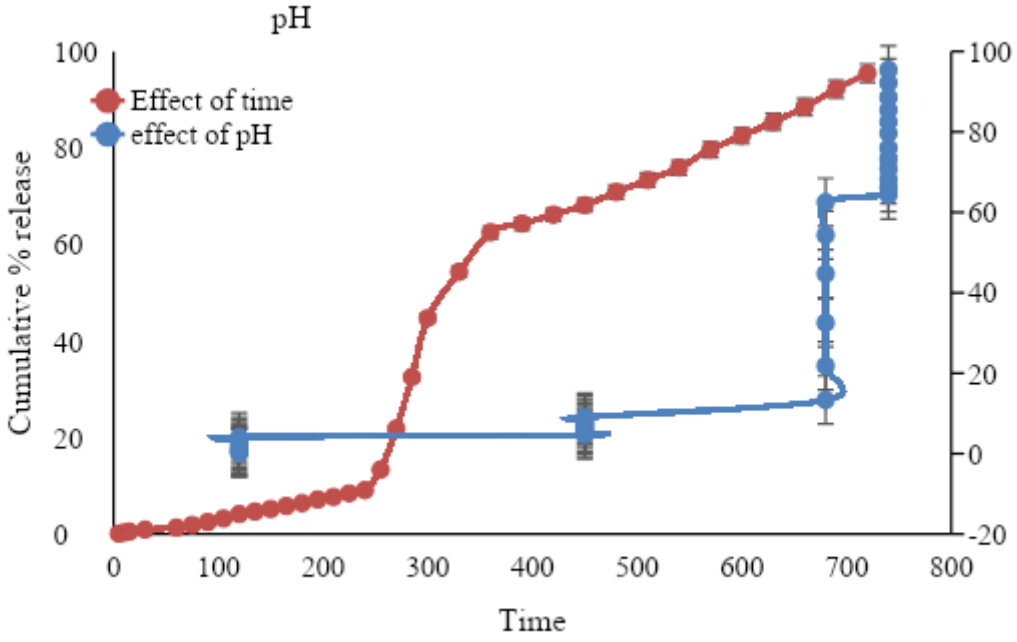

Figure 2: Effect of time and pH in the *in vitro* release of carvedilol from Zn-Fe nanospheres.

has been expressed in Figure 2. Only 9.08% of drug release had happened in the first 2 hr. This cumulative percentage had increased to 95.47 % after 12 hr.

Kinetic Studies on Continuous Release of Carvedilol Loaded Zn-Ferrite

For the kinetic studies the graph was plotted for a) Q vs t (Zero order kinetics) b) log cumulative % of drug release vs t (first-order kinetics) c) cumulative % of drug release vs $t^{1/2}$ (Higuchi model) d) log cumulative % of drug release vs log t (Korsmeyer -peppas model). By comparing the regression coefficient of all the models, Korsmeyer-Peppas model has given the best fit (R^2 = 0.934). The release exponent value of 0.15 has been obtained from the model and it indicates Quasi-Fickian diffusion.

Pre-formulation studies of capsule formulation

Before being loaded with the drugs, the capsules' physical characteristics were examined. The results reveal that the granules has excellent flow properties within the prescribed limits in pharmacopoeias and also of standard quality within safe limits.

Particle Size Analysis

The homogeneity of powder blends is greatly influenced by particle size. Zn-Ferrite NSs has 262.8 nm size and 0.19 polydispersity, whereas for drug loaded Zn-Ferrite average particle size is 247.6 and 0.20 polydispersity. It is important to properly regulate the particle size to achieve continuous powder flow.[47]

Organoleptic Properties of Zn-Ferrite NSs

The physical appearance of organoleptic properties of the Cardevilol drug-loaded Zn-Ferrite NSs is crystalline, free-flowing, small particulate powder, of greayish black in colour with a characerstic odour.

Thermal Stability

The thermal stability of the Zn-Ferrite NSs and the nanospheres loaded with carvedilol drug has been studied with DSC and TGA. The mass loss observed initially was due to loss in moisture in both the nanospheres and the drug-loaded nanoparticles at 300°C. The transition of phase change has been observed in DSC analysis between 110 to 135°C. Due to this change of phase, a reduction of weight is observed in TGA at 275°C. The destruction of the nanospheres loaded in the drug was observed at 200 and 998.2°C.

Evaluation of Filled Capsule

The capsules were hand-filled with carvedilol drug and the evaluation parameters like weight variation, dissolution and disintegration time of finished capsules were performed. The weight variation test shows that the average weight of content present in the capsules is 247.4 mg with an average disintegration time of 11.60 min. The dissolution studies shows that that 93.48% drug release for a time period of 24 hr.

As shown in Figure 3 the drug release from the mesoporous Zn-Ferrite NSs was about 93.48% for a time period of 24 hr. It was found that the release of the drug from the drug-loaded

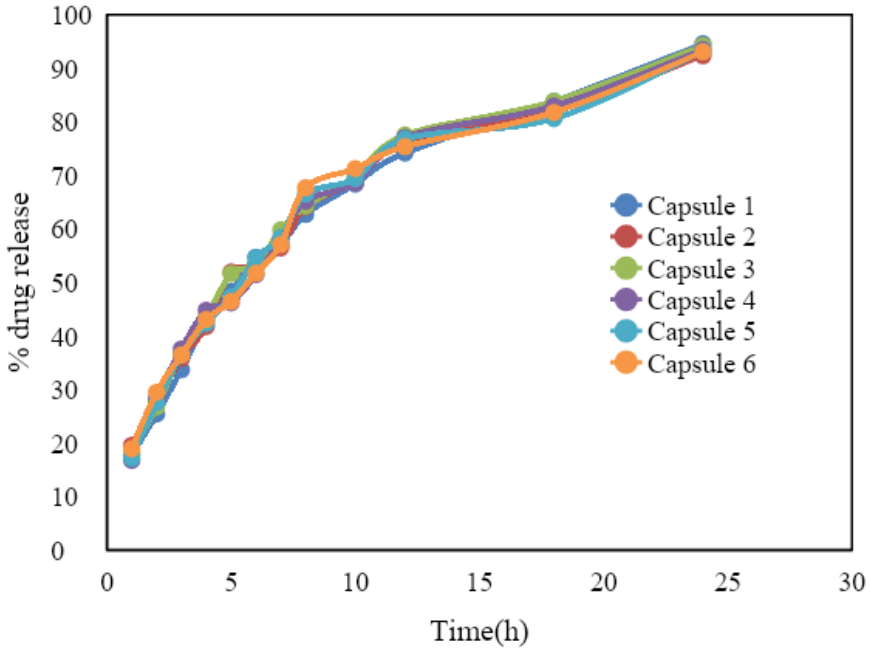

Figure 3: Effect of time on drug release (%).

Table 1: Comparative Analysis with Previous Studies.

Study	Nanocarrier	Encapsulation efficiency (%)	Drug release (%)	Release kinetics model
Cui *et al.*, (2022)	Fe_3O_4	72.1%	85.3% (12 hr)	Higuchi Model
Sun *et al.*, (2023)	$MnFe_2O_4$	78.5%	88.2% (12 hr)	First-Order Model
This Study	Zn-Ferrite	84.6%	95.47% (12 hr)	Korsmeyer-Peppas Model

Zn-Ferrite NSs was found to follow a controlled or sustained release for a period of 24 hr.

DISCUSSION

TEM analysis shows a homogenous size distribution with a symmetrical shape and mesoporous crystallinity was also observed.[21] As visualised in the image all the particles are mostly spherical in shape with a single core-shell structure. The XRD peaks were discovered to be in good agreement with the typical pattern of cubic $ZnFe_2O_4$ with a spinel structure (JCPDS file no. 22-1012). The crystal size of the polymer functionalized $ZnFe_2O_4$ nanosphere[28] was calculated based on Full Width at Half-Maximum (FWHM) at (311) peak by applying the Scherrer equation, which was observed at 24.60 nm. The negative zeta potential observed could be attributed to the binding of functional groups onto the nanoparticles surface, suggesting the presence of repulsive electrostatic forces. Also, the positive charge on the surface of the Zn-Fe_2O_4 nanocarrier is useful for higher drug loading and allows controlled delivery of the drug. The drug-loaded polymer functionalized Zn-Ferrite (1:5 ratio) had a high percent of drug loading[17] due to a high percent of decomposition was compared with pure Zn-Ferrite carrier. DSC reveal that the drug-loaded Zn-Ferrite at different ratios melting exothermic peak implied that the drug had been incorporated both on the surface and inside the porous $ZnFe_2O_4$ nanosphere carrier and it had high stability.[31]

pH also played a major role in the drug release. No big increments were noticed between the pH range of 1 to 5. But a sudden incline in the cumulative release (%) was observed after 6.8pH, and the maximum release was observed at 7.4 pH. Kinetic analysis indicated that the drug release followed the Korsmeyer-Peppas model, and it indicates Quasi-Fickian diffusion.[32] In thermal stability studies, a prominent peak for the drug was not observed in the DSC analysis and a slight shift was noticed in TGA analysis. Both of these observances are due to the proper entrapment of the drug onto the nanospheres and the stability of this composite is analysed.[48] *In vitro* drug release studies showed that the carvedilol-loaded Zn Ferrite nanospheres released the drug slowly, with 93.48% of the drug released over 24 hr, indicating high bioavailability.[49-52]

The encapsulation efficiency and release profile of Zn-Ferrite nanospheres were compared with Fe_3O_4- and $MnFe_2O_4$- based nanocarriers in order to assess the effectiveness of Zn-Ferrite nanospheres in drug encapsulation and release in comparison to prior studies. The results presented in Table 1 show that Zn-Ferrite offers a higher encapsulation efficiency and a more controlled drug release, which is attributed to its optimized surface chemistry and dispersion stability as well.

Comparing Zn-Ferrite nanospheres to pure medication, Thermogravimetric Analysis (TGA) demonstrated its heat stability. Rendering to the TGA curve, pure carvedilol degrades at 210°C, causing a significant weight loss. Nevertheless, Zn-Ferrite nanospheres loaded with drugs show a delayed weight loss beginning at about 275°C, suggesting enhanced thermal stability brought on by potent drug-polymer interactions. This implies that a key component of formulations for sustained drug release is the polymeric matrix's ability to shield the medication from early degradation.

Carvedilol's thermal stability within the Zn-Ferrite matrix is further supported by the Differential Scanning Calorimetry (DSC) analysis. Pure Carvedilol's DSC thermogram shows a distinct endothermic peak at 117.92°C, which is also its melting point. The drug-loaded Zn-Ferrite nanospheres, on the other hand, exhibit a wider peak in the 110-135°C range, suggesting that the drug has partially amorphized and that its interaction with the carrier has improved. This change demonstrates how well Carvedilol was encapsulated in Zn-Ferrite, lowering crystallinity and enhancing solubility.

CONCLUSION

Zn Ferrite were fabricated through a solvothermal method and subsequently loaded with carvedilol. Characterization studies, including particle size analysis, were conducted, revealing comparatively high particle size and zeta potential. The capsules were loaded with different weights (%) of the drug, and the organoleptic studies were also carried out. Studies on the *in vitro* release of the drug have shown a slow release of the drug with high bioavailability. 93.48% of the drug had been released sustainably for a period of 24 hr. Kinetic studies on drug release have shown Korsmeyer-Peppas model was found to be more significant. Carvedilol-loaded Zn-Ferrite nanospheres met all required standards, suggesting efficient utilization for Cardiovascular Disease (CVD).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

APCs: Antigen-presenting cells; **ATS:** Aminopropyl triethoxy silane; **BCS:** Biopharmaceutics Classification System; **CNTs:** Carbon nanotubes; **CVD:** Cardiovascular disease; **EDAX:** Energy dispersive X-ray analysis; **FTIR:** Fourier transforms infrared spectroscopy; **MNPs:** Magnetic nanoparticles; **MRI:** Magnetic resonance imaging; **NSs:** Nanospheres; **PIBMS:** Poly (isobutylene:co:maleic acid) sodium; **PTS:** Polyoxyethanyl-α-tocopheryl sebacate; **SEM:** Scanning electron microscopy; **TEM:** Transmission electron microscopy; **TGA:** Thermo Gravimetric Analysis; **TMPGS:** DL-α-Tocopherol methoxy polyethylene glycol succinate; **TPGS 1000:** D-α-Tocopherol polyethylene glycol 1000 succinate; **XRD:** X-ray diffraction.

ETHICAL STATEMENT

Neither human nor animal experimentation is used in this study. Every experiment followed institutional biosafety and ethical norms and was carried out *in vitro*. Good laboratory techniques were followed throughout the study to guarantee repeatability and scientific integrity.

SUMMARY

Zn-Ferrite nanospheres were synthesized using a solvothermal method. XRD, FT-IR, HR-SEM, and TEM were used to characterize the synthesised nanospheres reveals the particle size and high zeta potential. Various drug loading percentages were tested, and organoleptic studies were conducted. The release of carvedilol from nanospheres was studied using dialysis method *in vitro*. The sustained Carvedilol release of 93.48% was observed at the end of 24 hr and it follows Korsmeyer-Peppas kinetic model.

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