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Chapter

Nanoferrites-Based Drug Delivery Systems as Adjuvant Therapy for Cancer Treatments. Current Challenges and Future Perspectives

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Abstract

Cancer is the second cause of death worldwide, whose treatment often involves chemotherapy. In a conventional therapy, drug is transported (and usually absorbed) across biological membranes through diffusion and systemic transport. The pathway that medicine must travel before reaching the desired location, can bring adverse or unwanted effects, which are mainly the result of: low bioavailability, low solubility and toxicity. To avoiding risks, nanoparticles coated with the drug could be used as a therapeutic substance to selectively reach an area of interest to act without affecting non-target cells, organs, or tissues (drug delivery). Here, the goal is to enhance the concentration of the chemotherapeutic drug in the disease parts of the body. Among all nanostructured systems, ferrites attract worldwide attention in drug delivery applications. It is due to their versatile magnetic and physicochemical properties. Here, it is reviewed and analyzed recent advances in synthesis, morphology, size, magnetic properties, functionalization with a focus in drug delivery applications of nanoferrites.

Keywords: Ferrites, Nanostructures, Functionalization, Drug-loading, Drug delivery, Cancer

1. Introduction

Cancer is a disease originating from unregulated cell growth. Those cells can spread throughout the body, causing erroneous behaviors in organs or tissues [1]. Cancer is one of the principal problems in public health and currently is the second leading cause of death worldwide. According to the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC), there are many types of cancer treatments. Treatment or therapy depends on the cancer, as well as its stage of progress. Most individuals with cancer receive a combination of treatments, such as surgery with chemotherapy and/or radiation therapy [2]. Chemotherapy is crucial in the prevention of tumor recurrence and progression. Some patients have been treated with chemotherapeutic agents (e.g., Doxorubicin, Cyclodextrin, Cisplatin, Taxanes, Gemcitabine, among others) for long-term survival.

Despite recent advances in treatments for various types of cancer, the recurrence rate and severe side effects still are a problem. To improve the life quality of cancer patients, more efficient and accurate targeting treatment is an urgent need.

A nanotechnology-based drug delivery system may provide a feasible means to solve the previous challenges. This kind of technology can be a formulation or device that enables a therapeutic substance to selectively reach an area of interest to act without affecting non-target cells, organs, or tissues [3]. One of the most studied, promising, and simplest ways to transport pharmaceutical compounds in the body is using nano entities as delivery vehicles [4]. Moreover, some nanoparticulated systems exhibit sensitivity to external stimuli, such as visible light, near-infrared light, ultrasound, AC or DC magnetic fields, among others. These stimuli could be made use as a tool to flexible control of dose magnitude and timing from the responsiveness (triggered remotely) [5].

Specifically, nanoferrites have been attracted worldwide scientific community attention for applications against cancer due to [6]:

- Their great potential for hyperthermia treatments.

- The possibility to guide nanoparticles to specific regions using an external magnetic field.

- The chance to remotely activate the drug release in a controlled way (alternating magnetic fields).

Ferrites are compounds derived from iron oxides, whose composition allows tuning the magnetic properties. According to the magnetic atoms disposition and its chemical environment, material can manifest hard of soft magnetic properties. Nanostructure ferrites have received the most attention for drug delivery applications due to their versatile magnetic and chemical properties [7].

Previous reports have pay attention to the use of nanoferrites in biomedical applications for:

- Improving magnetic resonance imaging sensitivity [8].

- Effective targeted treatment of lung cancer [7].

- Magnetite nanoparticles as an advanced platform for cancer theranostics [9].

- Hydrogel beads-based nanoferrites in novel drug delivery platforms [10].

- Magnetic and superparamagnetic ferrites for cancer therapy applications [11].

- Iron oxide and substitute ferrite nanoparticles in drug delivery [12].

- The toxicity of spinel ferrite nanoparticles [13].

- Biosensing platform on ferrite nanoparticles [14].

Thus, the chapter aims to correlate the morphology, size, ferrite type, magnetic properties, functionalization, and pharmacokinetics. These correlations allow obtaining a perspective to the physical targeting precision for cancer drug delivery applications. Furthermore, we also discussed the current challenges and future perspectives of nanoferrites in the field of oncology.

2. Size, morphology, and magnetic properties of nanoferrites for drug delivery in cancer

The size, morphology, and magnetic properties of nanoparticles in drug delivery applications, have been identified as keys parameters in the literature [1, 2]. The easy way to tune these properties is from the synthetic routes [15]. The growth mechanism involved in the final morphology and structure is not completely clear. The conditions synthesis and their correlation with the physicochemical properties have been discussed in the literature [16]. Here, we focus on the recent advances in morphology, size, magnetic properties, and their relationship with the synthetic routes of nanoferrites used in drug delivery for cancer. **Table A1** shows a summary of these properties recently reported in the literature. For there, it is clear that the synthetic routes more employed for nanoferrites synthesis are:

- *Chemical coprecipitation:* it is a straightforward and inexpensive method. In this case, the precursor salts solutions containing the cationic metals are mix into an alkaline medium in a stoichiometric proportion.

- *Hydrothermal:* here, the chemical reactions take place in aqueous solutions at pressure and temperature higher than the room conditions.

- *Sol–gel*: the chemical reactions of hydrolysis and condensation are carried out of precursors in solution.
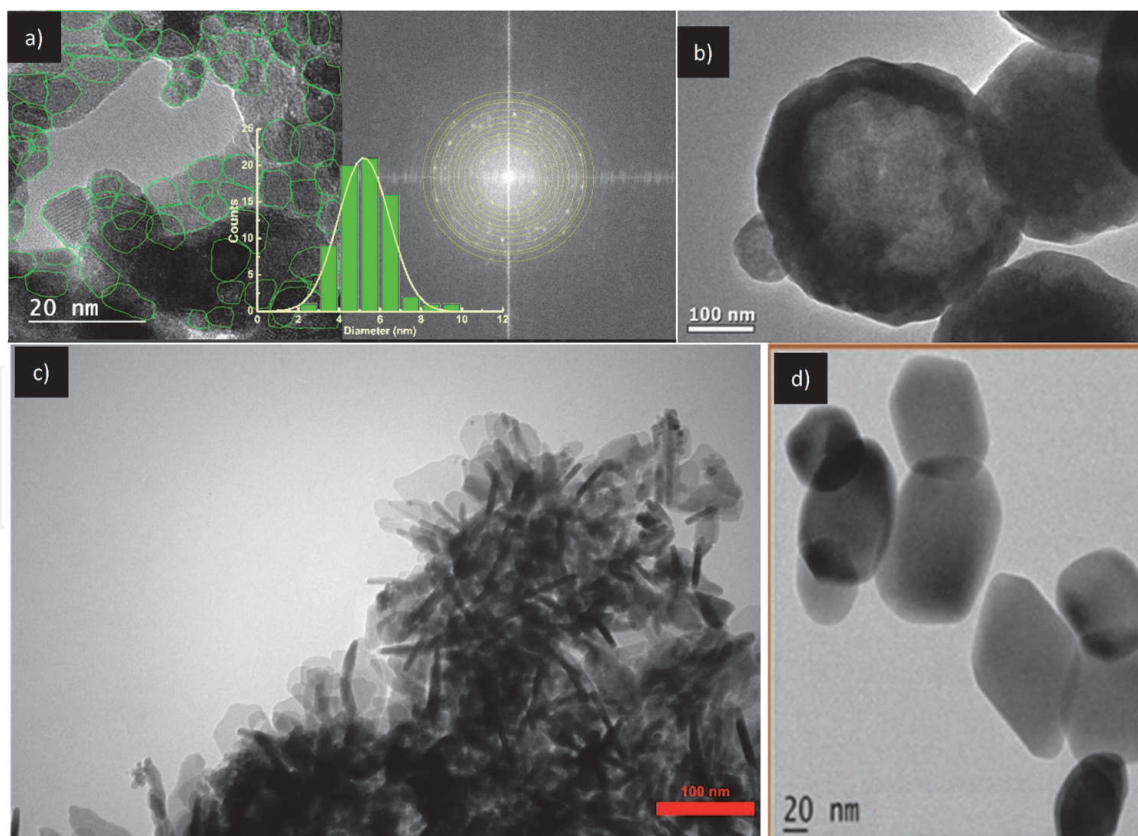

Figure 1.
Transmission Electron microscopy (TEM) images for a) calcium ferrite nanoparticles with a size of 5 nm, reproduced from Ref. [17] with permission of the editors, b) magnetite hollow spheres of diameter ~350 nm, reproduced from Ref. [65] with permission of the editors, c) magnetite nanorods, reproduced from Ref. [48] with permission of the editors, and d) magnetite hexagonal nanoparticles, reproduced from Ref. [56] with permission of the editors. Copyright 2019 MDPI, 2016 Nature, 2020 Elsevier, and 2021 the Royal Society of Chemistry.

- *Solvothermal*: it is like the hydrothermal technique. The difference is the use of nonaqueous solutions.

- Less popular synthesis techniques for nanoferrites obtention are thermal decomposition, sonochemical, thermal treatment, and thermolysis.

Tripathy et al. [14] reported a comparison among the different techniques for ferrite nanoparticles obtention.

Based on some scientific reports, nanoferrites used in cancer drug delivery applications range from 5.2 *nm* to 300 *nm* (**Table A1**). Calcium ferrite ($CaFe_2O_4$) obtained by coprecipitation is the smallest nanostructure system. Magnetite (Fe_3O_4) fabricate from the solvothermal method is the larger one (**Figure 1**). However, particles larger than 200 *nm* segregate by mechanical filtering and eventually get removed by phagocytic cells. Nanoparticles with sizes smaller than 10 nm lead to renal filtration and accumulation into the fenestration of the kidneys' glomerular endothelium. Therefore, the most effective drug delivery agents possess sizes ranging between 10 and 100 nm [68]. However, Sivaraj et al. [69] suggest that the nuclear membrane pores allow entry of nanoparticles with a size below 9 *nm*. Nanoparticles penetration into the cells may be maximized by surface functionalization with small molecules (e.g. folate, proteins, peptides, antibodies, and aptamers). This penetration induces receptor-mediated endocytosis, caveolae-mediated endocytosis, lipid raft mediated endocytosis, and/or micropinocytosis. After endocytosis in cancer therapy, nanomaterial releases maximum drug to inhibit the DNA/RNA synthesis and mitochondria damage.

The most common ferrite nanoparticles use for cancer drug delivery systems ranging from 20 *nm* to 30 *nm* (**Table A1**). Moreover, the most popular morphology

FT	Method	S	M_S	H_C	M_R	Reference
Fe_3O_4	Coprecipitation	11	59	0	—	[20]
$CoFe_2O_4$	Thermal decomposition	13	70.7	—	30.2	[22]
$MnFe_2O_4$	Sonochemical	13	34.9	0	0	[23]
Mn-Zn (Fe_2O_4)	Coprecipitation	15	56.0	0	0	[25]
$NiFe_2O_4$	Solvothermal	17	70	0	0	[29]
Fe_3O_4	Thermal treatment	23	7.1	143.8	2.2	[32]
Fe_3O_4	Coprecipitation	30	47.6	0	3.8	[39]
Fe_3O_4	Coprecipitation	35	36.3	0	—	[40]
Fe_3O_4	Coprecipitation	40	1.57	69.1	0.15	[41]
$CoFe_2O_4$	Coprecipitation	43	36.02	0	0	[42]
$GdFe_2O_4$	Coprecipitation	90	47	0	0	[57]
$CoFe_2O_4$	Solvothermal	104	51.8	0	0	[59]
$CaFe_2O_4$	Sol–gel	112	14.9	—	0.38	[61]
$MnFe_2O_4$	Coprecipitation	140	56.1	42.6	5.2	[62]
$CoFe_2O_4$	Thermolysis	200	51.1	0	0	[64]
$CoFe_2O_4$	Coprecipitation	250	40	1.7	—	[65]

Table 1.
Summary of spherical nanoparticles ferrite type (FT) obtained by different methods with their sizes (S in nm), saturation magnetization (M_S in emu/g), coercivity (H_C in Oe), and remanence (M_R in emu/g), reported in the literature. All the magnetic properties were reported at room temperature.

obtained from the synthetic routes is spherical particles (**Table 1**). Nanorods and particles with hexagonal shapes are the less common nanostructures used for drug delivery in cancer applications (**Figure 1**).

A complete understanding of magnetic properties is essential for a proper implementation of nanoferrites in drug delivery applications [6]. The saturation magnetization (M_s), coercive force (H_C), and remanence (M_R) are the most popular magnetic parameters reported for nanoferrites to cancer drug delivery applications (**Table A1**). Nanoferrites with the highest magnetic response (M_s) are cobalt ferrite ($CoFe_2O_4$) with a size of 15 nm obtained by sonochemical technique [28]. The smallest saturation magnetization was reported to zinc ferrite ($ZnFe_2O_4$) nanostructures (75 nm), which were synthesized by the sol–gel method [53]. Usually, nanoferrites used in cancer drug delivery applications show superparamagnetic behavior. Superparamagnetic nanoparticles evidence zero coercivity and remanence at temperatures above the blocking one (**Table 1**). In other cases, ferrite nanostructures with coercivity as high as 3409 Oe are used in cancer drug delivery applications ($CoFe_2O_4$ nanofibers with a diameter of 50 nm [45]. Moreover, cobalt ferrite nanoparticles show the highest magnetic remanence of 30.2 emu/g with a size of 30 nm obtained by thermal decomposition (**Table 1**).

3. Nanoferrites functionalized and functional groups for drug delivery in cancer

Non-functionalized nanoferrites (non-coating material on their surface) seems to be not optimal for drug delivery application. Surface energy minimization processes can promote agglomeration, percolation as well as other unwanted effects. Some of the most common problems whit this kind of nanosystems are [12]:

1. Agglomeration due to the attractive forces leading to non-stability of the nanoparticle dispersion.

2. Toxicity represents a problem in bare nanoferrites when they use without functionalization.

3. Bare nanoparticles do not have a functional group on their surface. This makes it hard to link drugs molecules.

To deal with these problems, nanoparticles have been coating with organic or inorganic molecules (functionalization). The surface engineering of ferrites could be accomplished during nanoparticle synthesis (in-situ) or after this (ex-situ). A detailed review of the coating and functionalization strategies was reported for nanoparticles in drug delivery applications by Pinelli et al. [70]. The surface functionalization procedure and choice of appropriate solvent are crucial factors for obtaining nanoferrites. Here, the repulsive interactions among nanoparticles prevent agglomerations [71]. Moreover, functionalization promotes several advantages such as stable dispersions, biocompatibility, biodegradability, and reduced toxicity. Usually, functionalized nanoparticles loaded with drugs adopt covalent/noncovalent interaction methods. Conjugation of a drug to a carrier by non-biodegradable linkages results in: changing the drug chemical units, reducing drug efficacy, and displaying relevant side effects. The drug remains unharmed by using physical adsorption for drug conjugation, and no changes occur in the chemical units and the controlled drug release behavior. In this case, the idea deals with functionalized nanoparticles that have an opposite electrical charge to the cancer

drug to promote the electrostatic interaction [42]. Moreover, surface functionality gives significant strength to bind and adsorb cancer drugs using specific functional groups. The characterization techniques for studying the functional groups attached to nanoparticles for drug delivery applications have been reported previously [12].

Some examples of functional groups commonly used to functionalized nanoferrites in drug delivery applications are:

- The carboxyl functional group of the meso, 2–3-dimercaptosuccinic acid (DMSA), was used to functionalize cobalt ferrite nanoparticles [22].

- Magnetite nanoparticles functionalized with mesoporous silica (SiO_2) [58].

- Zinc ferrite nanoparticles coated with hydroxyapatite as an intermediate of the cancer drug [72].

- The carboxyl functional groups of citrate molecules use to functionalize manganese ferrite nanorods [24].

- Calcium ferrite functionalized with biomolecules (casein). The hybrid molecule combines the merits of both inorganic and organic counterparts [61].

The functionalization can allows high drug encapsulation, stabilizes the nanocarrier, and reaches the cancer site-specific. Furthermore, the coating uses to reach the target cells without getting removed by the reticuloendothelial system of the body and to have a capable surface for keeping the drug unharmed until reaching the location of interest. The performance enhancement achieves through functionalization with suitable ligands that will bind to the aimed receptors of pathological tissues. The size of the nanocarrier has paramount importance for rendering it absorbable by tumor tissues [68]. The inclusion of active targeting functionalities results in drug accumulation within tumors, tumor cells, or immune cells and allows for reduced dosages due to specificity. Functionalized ferrite nanoparticles have been used for: a) imitate ligand binding to receptors, b) for initiation of cellular signaling, c) for increased stimulation of immune cells to better infiltrate and extinguish immunosuppressive tumors [73]. Commonly, the pH of cancer cells (tumor) is acidic ranging between 4 and 5. It is due to the presence of lactic acid, which starts due to inefficient consumption of glucose [74]. On the other hand, the pH in an extracellular matrix or bloodstream is natural (pH = 7) [75]. This difference in pH offers to fabricate functionalized nanoparticles as a pH-sensitive trigger for drug delivery applications.

The most popular drugs for cancer delivery applications, using ferrites as nanocarriers are: Doxorubicin [58], 5-Fluorouracil [21], Docetaxel [76], Hesperidin and Eugenol [60], Curcumin [77], Tamoxifen [55], Cisplatin [78], Nilotinib [79], Camptothecin [38], and Telmisartan [20]. Hydrophobicity of the orally administered drugs for cancer treatments has low systemic bioavailability [80]. It produces low water solubility and can cause serious adverse effects [62].

Among functionalized nanoferrites investigated to load cancer drugs, one can find:

1. Zinc ferrite functionalized with Polyethylene Glycol (PEG) and chitosan loaded with Curcumin [80]. Chitosan takes cationic amine functional groups, at low pH, which would involve an ionic gelation process with polyanions to form nanoparticles. It is used as an effective drug carrier, where the reactive amine groups on the chitosan side chain are used for functional group modifications. The hydrophobically modified chitosan improves the encapsulation efficiency of the carrier towards the hydrophobic drugs [34].

2. Cobalt ferrite nanoparticles functionalized with DMSA used the amine functional group of Doxorubicin molecules. Here, it is attached through electrostatic interaction and/or hydrogen bonding interactions with the carboxylic functional group of the DMSA [22].

3. Magnetite nanoparticles functionalized with mesoporous silica used the amine group of Doxorubicin to attach [58].

4. Zinc ferrite nanoparticles functionalized with hydroxyapatite had covalent bonds with the zoledronic acid drug. Amino or hydroxyl functional groups presented in hydroxyapatite are a strong chemical bond with the mineral material of bone phases [54].

5. Magnetite nanoparticles functionalized with gelatin using the functional groups $-NH^{3+}-$. It produces by partial hydrolysis of collagen to interact with Doxorubicin [81].

6. Calcium ferrite nanoparticles functionalized with biomolecules (casein), which allows the conjugation of targeting ligands with functional groups. Actively bind with specific receptors that may be overexpressed on tumor cells, allowing improved biodistribution and delivery of the drugs at the cancer site [61].

7. Manganese ferrite nanorods functionalized with citrate molecules to electrostatically attach Doxorubicin [24].

Proteins are promising carriers for drug delivery applications. The main advantages are the abundance of active sites, improved biocompatibility, easy availability, and pH-dependent swelling behavior. The last one allows the programmed release of the cytotoxic agent in response to the acidic cancer microenvironment [82].

DFT calculations demonstrated Cisplatin on graphene oxide can be adsorbed by the functionalized nanoferrites. Here, hydrogen bonds forming with hydroxyl and epoxy functional groups. It involves the formation of the amide bond between Cisplatin and the COOH functional group of graphene oxide. In the case of glutaraldehyde, the functional group is CHO, which formed the amide bond between Cisplatin and the CHO functional group [18].

4. Drugs loaded on functionalized nanoferrites for cancer treatments

Drug-loading of nanoparticles plays an essential role in drug delivery systems. There are several ways through which the drug can load with the functionalized nanoparticle:

- *Encapsulation*. It can entrap inside the nanoparticle.

- *Functionalization*. It can coat the surface of the nanoparticle.

- *Chemically linked*. It can be bond with the functionalized particle itself.

The second key point in functionalized nanoparticles design is the necessity to provide the nanoparticles with specific properties. The interaction with the external environment in the human body increases the targeting action towards determined sites [70].

Drug-loading involves several variables such as the solvent type and amount of it, the temperature, time of loading, and the drug-loading capacity. The most popular solvent for drug-loading is water (see **Table A2**). Less popular solvents involved in drug-loading are ethanol, dichloromethane, and saline solution. Usually, the solvent quantity varies from 1 *ml* to 200 *ml*. The drug-loading capacity represents the amount of drug loader per unit weight of the nanoparticle. Drug-loading represents the percentage of the nanoparticle mass that is due to the encapsulated drug. Loading capacity can calculate by the amount of total entrapped drug divided by the total nanoparticle weight. The drug-loading values reported for nanoferrites ranging from 0.016 [64] to 3.3 [63]. These values correspond to cobalt ferrite loaded with Doxorubicin and Docetaxel, respectively. The loading-drug temperature ranges from 4°C [54] to 55°C [33].

From **Table A2** many reports did not include the drug-loading solvent, the solvent quantity, and the drug loading capacity. The efficiency of drug-loading measure by a high-performance liquid chromatography system (HPLC) [30] or ultraviolet–visible spectroscopy (UV–Vis) [18]:

$$Drug - loading\% = \frac{total\ amount\ of\ drug - free\ amount\ of\ drug}{total\ amount\ of\ drug} x100 \qquad (1)$$

The free amount of the drug is measure by the absorbance of the supernatant in a UV–Vis spectrophotometer at the maximum wavelength of the dissolved drug. The nanoferrites can magnetically remove from the solution instead of the centrifugation process. The maximum wavelength for anticancer drugs are: Doxorubicin at 479 *nm* [23], Curcumin at 425 *nm* [34], Camptothecin at 480 *nm*, [68], 5-Fluorouracil at 266 *nm* [21], Cisplatin at 300 *nm* [18], Imanitib at 260 *nm* [31], Telmisartan at 296 *nm* [20], and Tamoxifen at 250 *nm* [55].

The time of loading is one of the essential factors in drug-loading. **Figure 2** shows a summary of the drug-loading efficiency results reported in the literature. The highest efficiency for drug-loading (98,3%) is reporting for calcium ferrite loaded with Curcumin in ethanol solvent at 100 *mL* with a drug-loading capacity of 0.4, at room temperature for 3 *h* [34]. The lowest efficiency for drug-loading (8,4%) is reporting for cobalt ferrite. It is loaded with Docetaxel in 10 *mL* of dichloromethane at room temperature for 1 *h*.
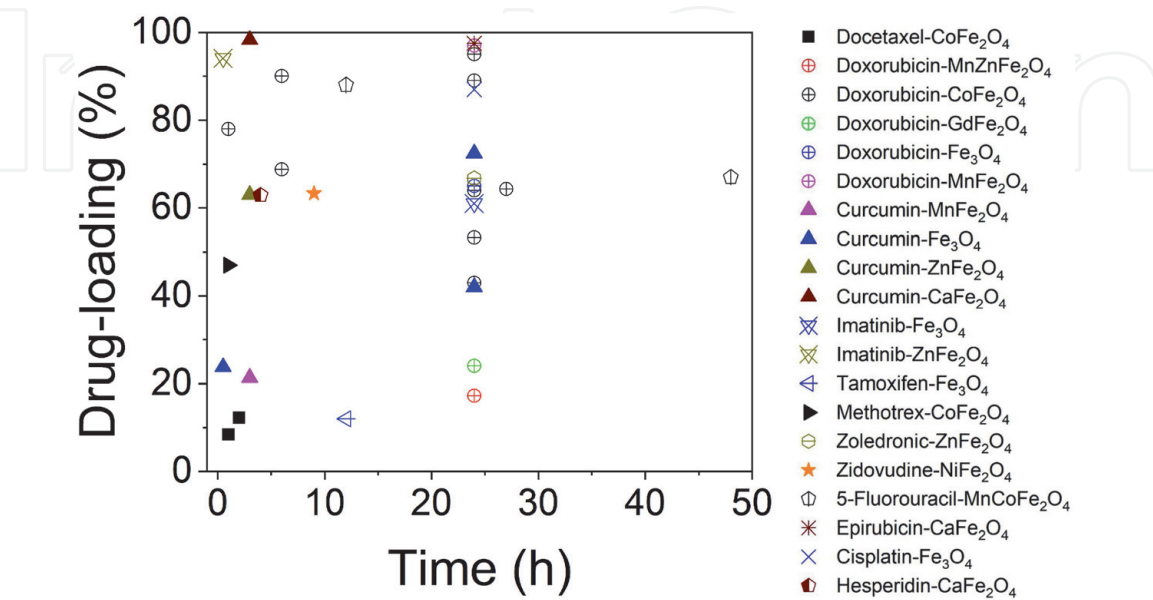

Figure 2.
Summary of the drug-loading percentage as a function of the time reported in the literature. All the data plotted are shown in **Table A2**.

Other alternatives for drug-loading of nanoferrites composites include:

1. Anchored nanoferrites of cobalt [28] and manganese [23] on graphene oxide were developed for controlled drug delivery nanocomposites.

2. Doxorubicin and nickel ferrite nanoparticles were incorporate into N-carboxymethyl chitosan/poly(ε-caprolactone) nanofibers for drug delivery applications [51].

5. Drug delivery of functionalized nanoferrites for cancer treatments

Conventional drug delivery methods rely on the absorption of drugs and transport across biological membranes through diffusion and systemic transport. The targeted drug delivery, on the contrary, focuses on enhancing the concentration of the chemotherapeutic drug in the disease parts of the body [87]. The drug release studies, usually, are realized in simulated physiological conditions and measured by HPLC [30] or UV–Vis spectra [88]. For UV–vis spectrophotometer, the percentage of release drug is given by [49]:

$$Drug\ release\% = \frac{amount\ of\ release\ drug}{amount\ of\ loaded\ drug} x100 \qquad (2)$$

The drug release mechanisms evaluate with different models, such as zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell. A detailed explanation of these five mathematical models to investigate drug release kinetic on *in-vitro* release data was reported by Jafari *et al.* [75]. The best mathematical model with a high correlation coefficient determines the suitable mathematical model and confirms drug release kinetics. Some results reported in the literature are summarized next:

- Curcumin drug loading on vanillin-chitosan coated with calcium ferrite hybrid nanoparticles as a carrier [34]. In most cases, the release mechanism follows non-Fickian diffusion, which may be due to the porous nature of the material, swelling ability, or the presence of an excess amount of surface adsorbed drug on the nanoparticles.

- Doxorubicin hydrochloride and Methotrexate drugs load on magnetite nanoparticles based on polyurethane matrices. The best fitting for the drug's release was the Higuchi kinetic model [75].

- Hesperidin drug loaded on magnetic casein-$CaFe_2O_4$ nanohybrid carrier conjugated with progesterone. Here, the release profile exhibiting the best fit towards the Higuchi model. Fickiand diffusion was validated as the release mechanism, which is a concentration gradient process [61].

- Doxorubicin drug loaded on carboxymethyl chitosan/poly(ε-caprolactone)/ doxorubicin/nickel ferrite core-shell fibers. Here, the Korsmeyer-Peppas model showed the best pharmacokinetic fit [51].

- Hesperidin and Eugenol drugs loaded on folic acid functionalized BSA-$CaFe_2O_4$ nanohybrid carrier. The Korsmeyer-Peppas model showed the best fit for releasing the drug. The release mechanism at pH 1.2 is by anomalous diffusion. It is a combination of Fickian diffusion and the gradual erosion of the

polymer. The release data for pH 5.8 and pH 7.4 fits well with the Higuchi model indicating a surface diffusion mechanism, in other words, the diffusion of the surface-bound [60].

- Cisplatin drug loaded on magnetite nanocomposite. The results of the kinetic studies suggest that the most proper model to interpret the release of the drug in pH 5.5 is the Korsmeyer-Peppas equation. The value of the release exponent in this model suggests that the prime mechanism of drug release is diffusion and Fickian [78].

- Doxorubicin drug loaded on pure and lanthanum doped bismuth ferrite nanostructures. The kinetic studies and adsorption isotherms revealed that the adsorption of the drug fitted well to the pseudo-second-order and Freundlich isotherm models. The adsorption of doxorubicin followed the multi-layered heterogeneous adsorption. The probable loading mechanism was electrostatic interaction [89].

The efficiency *in-vitro* tumor-targeted drug delivery of the nanoferrites loaded with anticancer drugs is evaluated by fluorescence microscopy imaging [58]. Here, the authors used human cancer cell lines as: MCF-7, A-549 [81], A431 [37], SKOV-3, MDA-MB-231 [61], SK-BR3 [33], MDA-MB-231, MCF-10A [90] in a culture media which is incubate in presence of the nanoferrites. Moreover, cytotoxicity determines the efficiency of the formulation [51]. The cytotoxic effect of the nanoformulation tests the cell viability (MTT) assay. It evaluated the ability of viable cells to reduce MTT to formazan crystals. The following equation used to calculate the % of cell viability is [91]:

$$\%Cell\ viability = \frac{average\ sample\ read}{average\ control\ read} x100 \qquad (3)$$

In-vivo antitumor therapy came tests in mice. Here, hepatoma cell lines (H22) inoculate into the back of the hind leg through subcutaneous injection. When the size of the tumor was grown to about 40 mm^3 were treated with the drug-loading nanoferrites. All the formulations were injected intravenously through the tail of mice. The tumor inhibition rates could be determined by fluorescence microscopy [67]:

$$Tumor\ inhibition\ rates = 1 - \frac{tumor\ volume\ with\ drug\ group}{tumor\ volume\ in\ control\ group} x100 \qquad (4)$$

Nanoferrites have got importance in terms of biological applications due to their physicochemical properties. To enhance their cancer therapeutic effect stimuli-responsive combine treatments have been developed:

- *Magnetic hyperthermia therapy.* Here, drug release may be activated applying an external alternating magnetic field which transforms electromagnetic energy into heat and induces the drug carrier to release its contents into the target site [34, 36, 57]. The combined techniques can enhance the therapeutic effect by increasing the blood flow and improving the oxygen supply to the tumor sites when increasing the temperature of the tumor sites from 37°C to hyperthermia temperature 42–45°C. This phenomenon can also enhance the drug delivery efficacy and increase the drug dosage to the target tumor sites. To determine the intracellular drug delivery of ferrite nanoparticles load with anticancer drugs, which were placed in dialysis membrane tubes and dialyzed at 37°C with different pHs [22].

- *Chemo-sonodynamic therapy.* It is another strategy for cancer treatment because the low-intensity ultrasound caused the activation of drug-loaded magnetic nanosonosensitizers. With synthesized ultrasound-sensitive nanocarriers, chemo-sonodynamic therapy is a generator of cellular reactive oxygen species, mitochondrial damage, and inducer effect through the release of the loaded drug in magnetic nanoferrite [53].

- *Photodynamic therapy.* Photodynamics is a method to treat cancer via light and photosensitizing chemical material. Here, small bandgap energy of the nanocarrier is desired to excite the electrons by light. The electrons transferred from the conduction band to the valence band produce an electron–hole pair. These pairs react with H_2O and O_2 and produce reactive oxygen species (ROS) [77].

- *Microwave irradiation*. Microwave irradiation added to magnetite nanocomposite increases the drug release [19].

Usually, drug delivery is dramatically pH-dependent. Most of the papers reported in the literature studied the influence of pH on the release behavior of the carrier. pH variations at different physiological situations trigger a controlled delivery of drugs at different sites. The pH-responsive drug release under three conditions of simulated gastric fluid (pH 1.2), cancer microenvironment (pH 5.4), and simulated body fluid (pH 7.4) during a determined time [61]. **Table A3** shows the influence of the pH on the release efficiency of the carrier. From there, in all cases, the acidic pH stimuli the rate of drug delivery. **Table 2** shows the drug release percentage at cancer microenvironment conditions for nanoferrite formulations. The time of drug release is one of the essential factors in drug delivery. **Figure 3**

System	pH	t (h)	T (°C)	DR (%)	Reference
Fe_3O_4 – Doxorubicin	5.5	80	37	60	[58]
$Mg_{0.5}Co_{0.5}Fe_2O_4$-5-fluorouracil	4.5	48	37	97	[21]
$CoFe_2O_4$ -Doxorubicin	5.4	75	37	42	[83]
$CoFe_2O_4$ -Doxorubicin	5.4	120	37	52	[47]
$CoFe_2O_4$-Hesperidin and eugenol	5.8	24	35	73.7	[60]
$MnFe_2O_4$ -curcumin	5.5	120	37	90	[60]
$CoFe_2O_4$ - Doxorubicin	4.0	24	37	60	[43]
$MnFe_2O_4$- Doxorubicin	5,5	10	37	17.16	[24]
Fe_3O_4 - Curcumin	5.0	120	37	40	[92]
Fe_3O_4 -Telmisartan	5.5	52	37	82	[20]
$ZnFe_2O_4$ - Curcumin	5.5	96	37	64.71	[53]
Fe_3O_4- Cisplatin	5,5	48	37	96	[78]
Fe_3O_4-Doxorubicin	5.8	72	25	70	[26]
$CoFe_2O_4$-Doxorubicin	5.4	72	37	80	[42]

Table 2.
Summary of drug delivery conditions and results reported in the literature for ferrite nanoparticles loaded with anticancer drugs (system). The main conditions are the cancer microenvironments (pH), the time (t), and the temperature (T) of release. The drug release (DR) percentage measures the efficiency of the process.
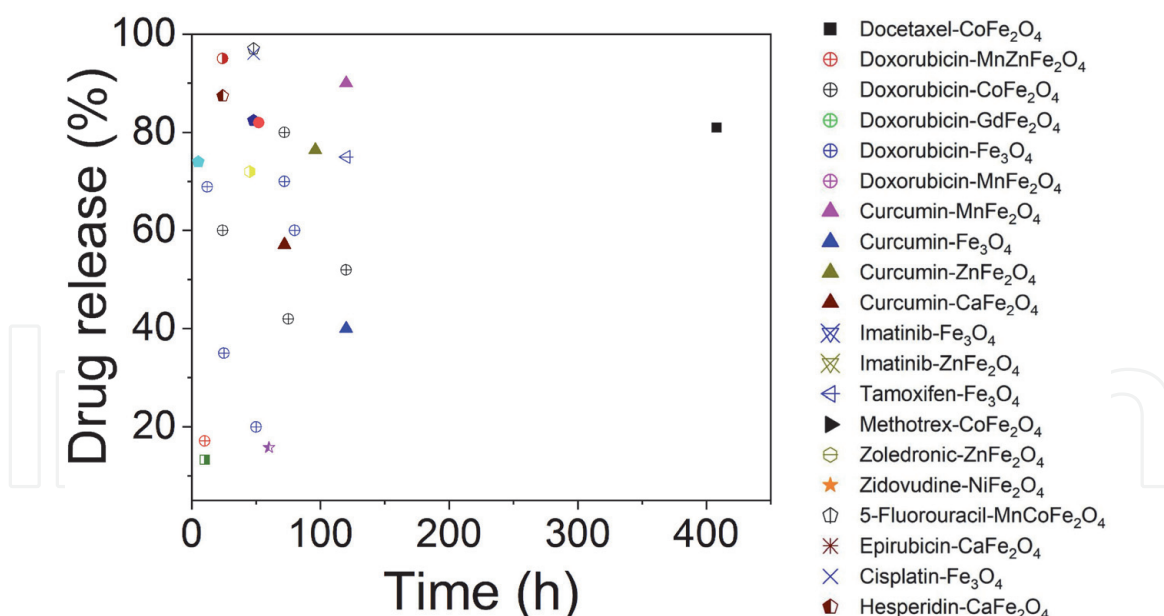
Figure 3.
*Summary of the drug delivery efficiency as a function of the time reported in the literature. All the data plotted are shown in **Table 2** and **A3**.*

shows a summary of the drug delivery efficiency results reported in the literature. The highest efficiency for drug delivery (97%) is reporting for magnesium-cobalt ferrite loaded with 5-fluorouracil for 48 h [21]. The lowest efficiency for drug delivery (8,9%) was reported for magnetite load with Curcumin for 37 h.

6. Conclusions

Recent advances reviewed on synthetic routes for the obtention of nanoferrites for drug delivery applications. The most popular ferrite is magnetite obtained by chemical coprecipitation method with sizes ranging from 20 nm to 30 nm, and spherical shape. Moreover, it reviews the magnetic properties of ferrite nanoparticles. Often, the nanoferrites are superparamagnetic. Coated the nanoparticle's surface with organic or inorganic molecules makes the nanostructures optimal for drug delivery applications. Functionalization reduces the agglomeration and toxicity of the nanoferrites. Physical adsorption among the functional groups of the cancer drugs and the coated molecules on the nanoparticles preserve the chemical structure of the medicament. Oncology drugs were detailed for drug delivery applications. The most popular solvent for drug-loading is water. It discussed the influence of parameters such as: pH, temperature, and time on drug-loading.

It reviewed the main drug release mechanisms for investigating pharmacokinetics. The release mechanism is highly dependent on the pH, the type of drug, and the nanocarrier. It discussed the stimuli-responsive combine treatments for cancer drug delivery applications. Some challenges persist:

- The nonspecific accumulation of the drug and the lack of real-time monitoring of the delivery.

- Develop novel multifunctional theranostic platforms with the abilities of intelligent controlled released and in-vivo site targeting delivery and treatment of illnesses.

- Improve the delivery effectiveness of a drug by maintaining the concentration of the drug between the effective and toxic levels.

- Inhibiting the dilution of the drug in the body fluids, and allowing targeting and localization of a drug at a specific site

- Determine the optimal temperature and concentration of drug required to promote effective apoptosis.

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Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

FT	Method	S (nm)	Mo	M_S (emu/g)	H_C (Oe)	M_R (emu/g)	R
Ca	Coprecipitation	5	Spherical	12.8	3.4	0.06	[17]
Fe	Coprecipitation	7	Spherical	—	—	—	[18]
Mn	Coprecipitation	10	Semi- spherical	13	12.9	0.15	[19]
Fe	Coprecipitation	11	Spherical	59	0	—	[20]
MnCo	Glycol-Thermal	12	Spherical	—	—	—	[21]
Co	Thermal decomposition	13	Spherical	70.7*	—	30.2	[22]
Mn	Sonochemical	13	Spherical	34.9	0	0	[23]
Mn	Hydrolysis	15	Nanorod	69.3	116	—	[24]
MnZn	Coprecipitation	15	Spherical	56	0	0	[25]
Fe	Coprecipitation	15	Spherical	—	—	—	[26]
Co	Coprecipitation	15	Spherical	—	—	—	[27]
Co	Sonochemical	15	Spherical	94	0	0	[28]
Ni	Solvothermal	17	Spherical	70	0	0	[29]
Ho	Hydrothermal	21	Spherical	47.8	—	—	[30]
Zn	Hydrothermal	21	Coral	2	0	—	[31]
Fe	Thermal treatment	23	Spherical	7.11	143.9	2.21	[32]
Ni	Sol–Gel	24	Spherical	—	—	—	[33]
Ca	Combustion of solutions	25	Spherical	9.11	—	0.02	[34]

FT	Method	S (nm)	Mo	M_S (emu/g)	H_C (Oe)	M_R (emu/g)	R
Co	Coprecipitation	26	Spherical	49	549	—	[35]
Co	Microwave heating	27	Spherical	90.5	830	—	[36]
Ca	Coprecipitation	30	Semi- spherical	58.3	—	—	[37]
Fe	Hydrothermal	30	Hexagonal	1.2	175	0.91	[38]
Fe	Precipitation	30	Spherical	47.6	0	3.81	[39]
Fe	Coprecipitation	35	Semi- spherical	36.3	0	—	[40]
Fe	Coprecipitation	40	Spherical	1.57	69.1	0.15	[41]
Co	Coprecipitation	42	Spherical	36.0	0	0	[42]
Co	Solvothermal	43	Spherical	47.7	—	—	[43]
Co	Coprecipitation	43	Spherical	62.4	—	—	[44]
Co	Precipitation	50	Nanofiber	3.9	3409	2.1	[45]
Co	Coprecipitation	50	Spherical	59.9	—	—	[46]
Co	Sol–Gel	50	Semi- spherical	64	—	—	[47]
Fe	Hydrothermal	50	Nanorods	22.2	0	—	[48]
Fe	Coprecipitation inverse	60	Spherical	63	—	—	[49]
Ca	Combustion of solutions	60	Spherical	9.1	—	0.02	[50]
Ni	Sol–Gel	70	Spherical	50.5	—	—	[51]
Ho	Hydrothermal	74	Semi- spherical	43	—	—	[52]
Zn	Sol–Gel	75	Spherical	0.6	65.6	3.8	[53]
Zn	Coprecipitation	80	Semi- spherical	31	100	—	[54]
Fe	Coprecipitation	80	Semi- spherical	80.1	—	—	[55]
Fe	Hydrothermal	90	Hexagonal	34	714	—	[56]
Gd	Coprecipitation	90.1	Spherical	47	0	0	[57]
Fe	Solvothermal	95	Spherical	59	—	—	[58]
Co	Solvothermal	104	Semi- spherical	51.8	0	0	[59]
Ca	Sol–Gel	112	Spherical	15	0.16	0.38	[60]
Ca	Sol–Gel	112	Spherical	15	—	0.38	[61]
Mn	Coprecipitation	140	Spherical	56.1	42.6	5.22	[62]
Co	Thermolysis	157	Spherical	13.7	0	—	[30]
Fe	Hydrothermal	200	Spherical	71.9	0	0	[63]
Co	Thermolysis	200	Spherical	51.1	0	0	[64]
Co	Coprecipitation	250	Spherical	40	1.7	—	[65]
Mn	Coprecipitation	300	Nanorods	18	—	—	[66]
Fe	Solvothermal	300	Spherical	57.4	57.5	—	[67]

Table A1.
Summary of nanoparticles ferrite type (FT) obtained by different methods with their sizes (S), morphology (Mo), saturation magnetization (M_S), coercivity (H_C) and remanence (M_R), reported in the literature (R). The magnetic properties were reported at room temperature.

FT	Drug	Sol	QS	LD	T(°C)	t(h)	%L	R
Co	D	D	10	—	RT	1	8,4	[30]
Fe	T	E	5	0.2	30	12	12	[55]
Co	D	W	30	3.3	RT	2	12,2	[63]
Ni	C	E	—	—	RT	12	—	[29]
Co	Do	W	5	—	—	1	—	[65]
Co	Do	W	25	0.04	25	24	—	[83]
Mn-Zn	Do	W	10	—	RT	24	17.3	[25]
Mn	C	W	25	—	RT	3	21,3	[84]
Fe	C	—	—	0.2	RT	0,5	23,7	[85]
Gd	Do	S	5	0.2	RT	24	24	[57]
Fe	C	W	10	0.2	RT	24	42	[48]
Co	Do	—	—	—	RT	24	43	[59]
Co	M	W	—	0.005	RT	1	47	[35]
Fe	C	W	25	0.3	RT	—	52,3	[32]
Co	Do	—	—	0.67	25	24	53,3	[42]
Fe	I	W	30	—	RT	24	61	[82]
Ca	H	E	—	—	RT	4	62,9	[40]
Zn	C	E	1	—	—	3	63	[60]
Ni	Z	W	20	—	55	9	63.2	[80]
Co	Do	—	—	—	RT	24	64	[66]
Co	Do	W	1	—	25	27	64.3	[33]
Co	Do	W	5	0.016	30	24	65	[43]
Fe	Do	—	—	0.5	RT	24	65	[27]
Zn	Zo	—	—	—	4	24	66,7	[64]
Mn-Co	5-F	—	—	—	RT	48	67	[58]
Co	Do	W	5	—	29.85	6	68,8	[54]
Fe	C	W	50	—	RT	24	72,4	[21]
Zn	C	W	50	0.016	RT	—	76,4	[71]
Co	Do	W	5	—	RT	1	78	[41]
Ca	Ci	—	—	—	25	—	86.5	[53]
Fe	Cis	—	—	—	RT	24	87	[86]
Mn	5-F	—	—	0.2	RT	12	88	[82]
Co	Do	—	—	—	RT	24	89	[18]
Co	Do	—	—	0.2	RT	6	90	[62]
Zn	I	—	—	0.42	45	0,5	94,0	[47]
Co	Do	S	200	—	37	24	95	[22]
Mn	Do	W	10	0.5	RT	24	97	[31]
Ca	E	—	—	—	37	24	97.5	[37]
Ca	C	E	100	0.4	RT	3	98,3	[34]

Table A2.
Summary of nanoparticles ferrite type (FT) loaded (Fe: Magnetite) with different anticancer drugs (D: Docetaxel, T: Tamoxifen, C: Curcumin; do: Doxorubicin, M: Methotrexate, I: Imatinib, H: Hesperidin, Z: Zidovudine, zo:Zoledronic acid, 5-F: 5-fluorouracil, ci: Cinnamaldehyde, Cis: Cisplatin, and E: Epirubicin,), the solvent (sol) used for loading (D: Dichloromethane, E: Ethanol, W: Water, and S: Saline solution) and the quantity (QS, in mL), the loading capacity (LD), the temperature (T), time (t, in hours), and percentage (% L) of loading, with their references (R).

System	pH	t (h)	T (°C)	DR (%)	Reference
Fe_3O_4 - Doxorubicin	7.4	80	37	20	[58]
$Mg_{0.5}Co_{0.5}$ Fe_2O_4–5-fluorouracil	6.5 7.4	48	37	73 73	[21]
Fe_3O_4- Docetaxel	7.4	48	37	82.43	[76]
$CoFe_2O_4$ -Doxorubicin	7.4	120	37	22	[47]
$CoFe_2O_4$- Hesperidin and Eugenol	1.2 7.4	24	35	87.44 54.29	[60]
$MnFe_2O_4$ - curcumin	7.4	120	37	41	[84]
$CoFe_2O_4$ - Doxorubicin	7.4	50	37.5	42.6	[43]
$CoFe_2O_4$ - Doxorubicin	7.4	24	37	30	[59]
$MnFe_2O_4$ - Doxorubicin	7.4	10	37	11.93	[24]
$CoFe_2O_4$ - Curcumin	7.4	72	37	57,1	[77]
Fe_3O_4- Curcumin	7.4	120	37	8,9	[92]
$CoFe_2O_4$ - Docetaxel	7.4	408	37	81	[30]
Fe_3O_4 -Telmisartan	7.4	52	37	25	[20]
$ZnFe_2O_4$ - Curcumin	7.4	96	37	76.45	[53]
Fe_3O_4 - Tamoxifen	7.4	120	37	75	[55]
$Ag_{(1-x)}NiFe_2O_4$ - Curcumin	6	5	31	74	[29]
$ZnFe_2O_4$ - Curcumin	6	15	38	—	[93]
$NiFe_2O_4$ -, $CoFe_2O_4$ - and Fe3O4 -Doxorubicin	7.4	0.0069	37	13.3	[71]
Fe_3O_4 - Cisplatin	7.4	48	37	93	[78]
Fe_3O_4 - Doxorubicin	6,86	25	—	35	[39]
Fe_3O_4 - Doxorubicin	7	72	25	35	[26]
$CoGd_xFe_{2-x}O_4$ - Curcumin	7.4	24	30	95	[94]
$CoFe_2O_4$ - Doxorubicin	7.4	72	37	80	[27]
$ErFe_3O_4$- Camptothecin	7.4	45	37	72	[38]

Table A3.
Summary of drug delivery conditions and results, reported in the literature for ferrite nanoparticles loaded with anticancer drugs (system). The main conditions are the pH, the time (t) and the temperature (T) of release. The drug release (DR) percentage measure the efficiency of the process.

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