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Review

The Potential Biomedical Application of NiCu Magnetic Nanoparticles

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Abstract: Magnetic nanoparticles became increasingly interesting in recent years as a result of their tailorable size-dependent properties, which enable their use in a wide range of applications. One of their emerging applications is biomedicine; in particular, bimetallic nickel/copper magnetic nanoparticles (NiCu MNPs) are gaining momentum as a consequence of their unique properties that are suitable for biomedicine. These characteristics include stability in various chemical environments, proven biocompatibility with various cell types, and tunable magnetic properties that can be adjusted by changing synthesis parameters. Despite the obvious potential of NiCu MNPs for biomedical applications, the general interest in their use for this purpose is rather low. Nevertheless, the steadily increasing annual number of related papers shows that increasingly more researchers in the biomedical field are studying this interesting formulation. As with other MNPs, NiCu-based formulations were examined for their application in magnetic hyperthermia (MH) as one of their main potential uses in clinics. MH is a treatment method in which cancer tissue is selectively heated through the localization of MNPs at the target site in an alternating magnetic field (AMF). This heating destroys cancer cells only since they are less equipped to withstand temperatures above 43 °C, whereas this temperature is not critical for healthy tissue. Superparamagnetic particles (e.g., NiCu MNPs) generate heat by relaxation losses under an AMF. In addition to MH in cancer treatment, which might be their most beneficial potential use in biomedicine, the properties of NiCu MNPs can be leveraged for several other applications, such as controlled drug delivery and prolonged localization at a desired target site in the body. After a short introduction that covers the general properties of NiCu MNPs, this review explores different synthesis methods, along with their main advantages and disadvantages, potential surface modification approaches, and their potential in biomedical applications, such as MH, multimodal cancer therapy, MH implants, antibacterial activity, and dentistry.

Keywords: NiCu magnetic nanoparticles; physical and chemical methods; surface modification; biomedicine; magnetic hyperthermia; curie temperature

1. Introduction

Magnetic nanoparticles (MNPs) attracted much interest in the last two decades, especially in the field of biomedicine. Their appealing potential biomedical applications rely on the strategic exploitation of their (extremely) small sizes, resulting in large surface areas, which distinguish them from bulk materials [1,2]. Additionally, MNPs have various unique magnetic properties, including their

superparamagnetic nature, a high magnetic susceptibility, a low Curie temperature (T_C), coercivity, and an inducible magnetic moment that allows them to be directed to a defined location or heated with an external alternating magnetic field (AMF) [3,4]. Among the properties that make MNPs ideal for biomedical applications are their biocompatibility, non-toxicity, and extensive aggregation in the desired tissue [5,6]. For their in vivo application, they must be coated by or encapsulated in a biocompatible polymer to prevent the formation of large aggregates, prevent the manipulation of their original structure, and potentially enable targeted biodegradation at the desired site in the body [7,8]. The important factors that determine the biocompatibility and toxicity of MNPs are the nature of the magnetically responsive component and the particles' final size, core composition, and coatings [9–11]. Moreover, MNPs with sizes below 100 nm are known to possess lower sedimentation rates and improved tissular diffusion [12,13].

The potential biomedical applications of MNPs require further consideration in regard to some specific properties. In addition to their composition of non-toxic and non-immunogenic materials, their sizes (and size distributions) have to be even more carefully controlled to prolong their circulation after injection in the body, as well as to allow them to pass through the capillary systems of organs and tissues to avoid vessel embolism. High magnetization is crucial for their movement in the blood so that they can be controlled using an AMF and immobilized close to the targeted pathologic tissue [2,14].

The abovementioned properties of MNPs and their ability to work at both cellular and molecular levels enabled their investigation and, in some cases, application in vitro and in vivo as part of drug delivery systems [15–17], in the targeted delivery of cytotoxic drugs [16,18,19], as active components in hyperthermia treatment [17,20,21], as contrast agents in magnetic resonance imaging (MRI) [1,22,23], as radiotherapeutics [24,25], for advanced gene delivery applications [26,27], for separation and selection [24,28], in magnetorelaxometry [29,30], as active antibacterial materials [31,32], in tissue engineering [8,33], and as part of biotherapeutics [34,35]. Figure 1 summarizes the potential applications of MNPs in biomedicine.

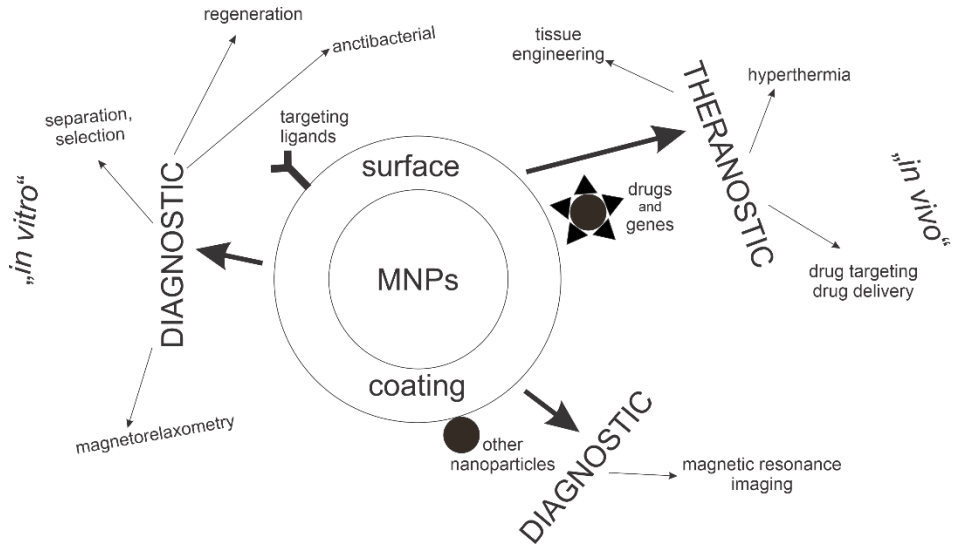

Figure 1. A schematic that illustrates the biomedical applications of magnetic nanoparticles (MNPs).

In the last decade, the authors of this paper developed several novel NiCu-based MNPs that not only exhibit all the above mentioned characteristics but also hold great promise for many different applications, which include multi-layer coatings, solar energy, and regenerative medicine, as well as in various formulations used in biomedicine [36–39]. The versatile range of potential applications, especially their applicability in biomedicine, is related to their chemical stability, proven biocompatibility with different human and animal cells, and tailorable magnetic characteristics. Their magnetic properties can be controlled using different preparation methods, ranging from mechanical milling, hydrothermal

reduction reactions, and emulsion techniques, through various electrochemistry-based and sol–gel methods, to plasma evaporation [36,40–42].

Despite the obvious potential of NiCu MNPs for biomedical applications, the general interest in their use for this purpose is rather low. Nevertheless, the steadily increasing annual number of related papers shows that increasingly more researchers in the field of biomedicine are studying this interesting formulation (Figure 2).

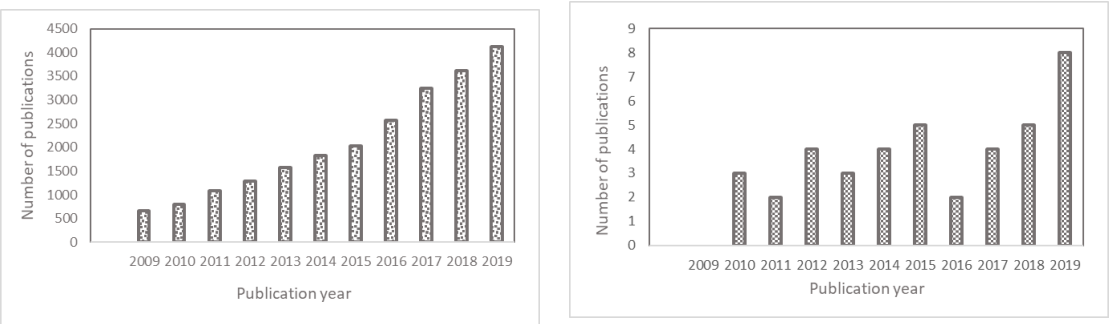

Figure 2. Research papers found using the keywords "MNPs AND biomedical applications" (left part of the figure) and "NiCu NPs AND biomedical applications" (right part of the figure). The number of papers is shown according to the year of publication. The data were obtained by searching the ScienceDirect search engine on 20 September 2019.

As is true for many other MNPs, NiCu MNPs were examined for their use in magnetic hyperthermia (MH) for the treatment of various cancers as their most interesting application type in biomedicine. For this purpose, biocompatible MNPs must be prepared. They are then applied to tumor tissues using different methods (e.g., controlled drug delivery) and subsequently heated in an AMF [38,43,44]. The heat produced through an AMF is influenced by various NP characteristics (size, shape, anisotropy, concentration in situ, and MH parameters, such as the frequency and field), which are all related (directly or indirectly) to their composition. The temperature to which the NPs are heated is defined by their Curie temperature (T_C) [39], which must be between 42 and 46 °C to maximize the selective damage to cancer cells without harming the surrounding healthy tissue [39]. This sometimes requires high frequencies, which represents an important limitation to the use of MNPs in MH [45]. For many years, most of the related research was performed on the two most well-known iron oxides (Fe_3O_4, γ-Fe_2O_3), although several other materials (e.g., Fe-doped Au NPs and $NiFe_2O_4$) were also developed and successfully employed for this purpose [39]. Furthermore, as shown in several studies, iron oxides are not without limitations, especially if adjustments to T_C play an essential role in therapeutic efficiency. Iron oxides tend to cause overheating because they have comparably higher *T*c values, which can induce damage to healthy tissues in the proximity of the application site [46]. This effect does not occur with NiCu MNPs, which have a tunable T_C that is much closer to optimal therapeutic temperatures [16,36,37]. In addition to the abovementioned investigations, research studies from the last couple of years showed that NiCu MNPs have great potential in several other types of biomedical applications, such as their use in bimodal cancer treatments that combine MH and controlled drug delivery [47–49]. Nevertheless, another important factor to be considered when applying a novel formulation for MH is the overall concentration of the respective NPs at the tumor site [50,51]. Specifically, NPs with a low specific loss power (SLP) need to be more concentrated in the tumor, with the consequent disadvantages of bioaccumulation and long-term toxicity [52,53].

In Section 2, this review explores different synthesis methods, along with their main advantages and disadvantages, potential surface modification approaches, and potential in biomedical applications, such as MH, multimodal cancer therapy, MH implants, antibacterial activity, and dentistry.

2. Synthesis of Magnetic NiCu NPs

Various kinds of synthesis methods, ranging from different chemical methods to physical methods, can be used for the preparation of NiCu MNPs. Figure 3 shows a graph that reveals the most commonly used methods, along with percentages of their application for the synthesis of NiCu MNPs according to the literature (the review was performed for the years 2004–2019).

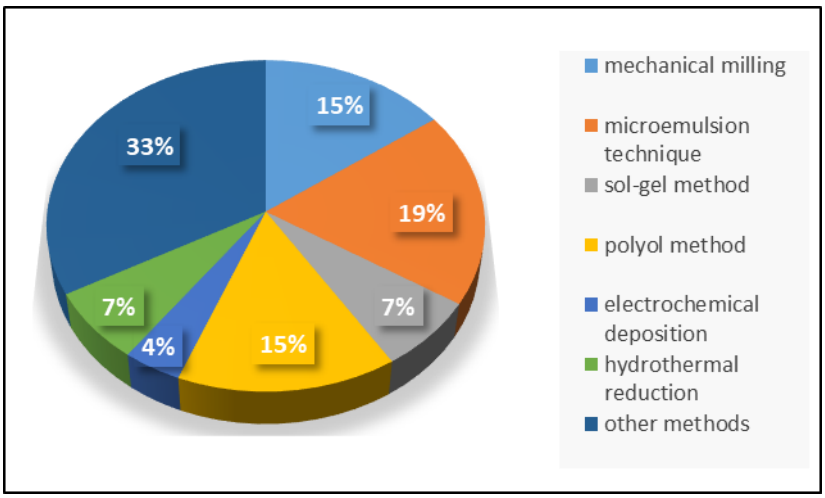

Figure 3. A comparative chart that depicts different synthesis methods of NiCu MNPs.

There are many differences between methods, especially in regard to the ability to control the particle size and the composition of the resulting particles. Furthermore, not all methods are environmentally friendly since they often rely on high temperatures and toxic chemicals (solvents and reducing compounds) and require multiple synthesis steps with low yields [54].

2.1. Mechanical Milling

Mechanical milling is a relatively simple non-equilibrium processing method in which various powdered components are mixed and milled in an inert atmosphere, resulting in the formation of NPs [55]. High-energy ball milling is widely utilized for the synthesis of various nanomaterials, nanograins, nanoalloys, nanocomposites, and nano-quasicrystalline materials. The whole process for this technique is based on the collision phenomena between the "balls" used and the powdered sample. During this process, the powdered particles in the sample are stuck between the colliding balls, which leads to particle deformation/fractionation and, hence, the formation of ultimately smaller particles in the resulting powder. The nature of these processes depends upon the mechanical behavior of the powder components, their phase equilibria, and the stress state during milling [55,56]. Figure 4 shows some examples of the mechanical milling method for the preparation of NiCu MNPs.

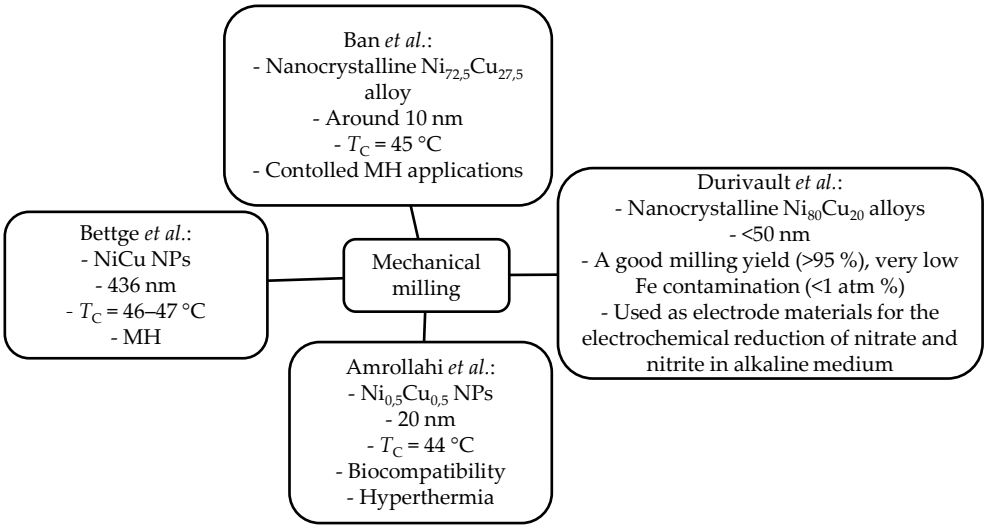

Figure 4. Mechanical milling as a method for the synthesis of NiCu MNPs MH—magnetic hyperthermia. The references to respective studies mentioned in the figure are as follows: Bettge et al. [48], Ban et al. [36], Amrollahi et al. [39], and Durivalt et al. [57].

2.2. Microemulsion Technique

In water-in-oil (W/O) microemulsion systems, fine microdroplets of the aqueous phase are trapped within assemblies of surfactant molecules (frequently in combination with a cosurfactant) dispersed in a continuous oil phase. The size of the reverse micelle is determined by the molar ratio of the water to the surfactant [3]. W/O microemulsions were shown to be an adequate, versatile, simple, and very fast procedure for preparing nanosized particles with a uniform size distribution. These are also the characteristics that could make this method useful for both in vivo and in vitro applications [2]. Figure 5 shows some examples of the microemulsion technique for the preparation of NiCu MNPs.

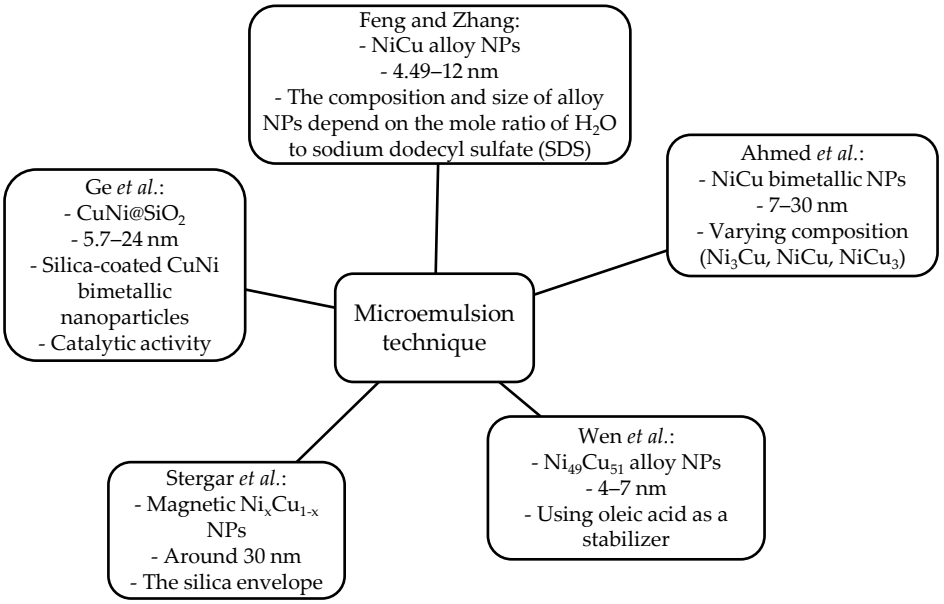

Figure 5. The microemulsion technique as a method for the synthesis of NiCu MNPs. The references to respective studies mentioned in the figure are as follows: Ge et al. [58], Feng and Zhang [42], Ahmed et al. [59], Stergar et al. [60], and Wen et al. [61].

2.3. Sol–Gel Method

The sol–gel method provides a very versatile approach to the preparation of new materials [62]. This method enables the potential control of the textural and surface properties of the resulting materials. In the sol–gel process, the final metal-oxide products are delivered after a few chemical steps: hydrolysis, condensation, and the drying process. The sol–gel method can be classified into two routes, namely, the aqueous sol–gel method and nonaqueous sol–gel method, depending on the nature of the solvent utilized [63]. Figure 6 shows some examples of the sol–gel method for the preparation of NiCu MNPs.

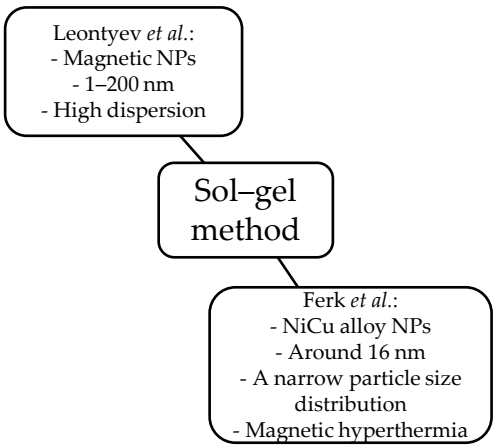

Figure 6. The sol–gel process as a method for the synthesis of NiCu MNPs. The references to respective studies mentioned in the figure are as follows: Leontyev et al. [64], and Ferk et al. [40].

2.4. Polyol Method

The polyol method involves the suspension of a metal precursor in a glycol solvent and the subsequent heating of the solution to a refluxing temperature [65]. This technique is used to synthesize metallic, oxide, and semiconductor NPs. A polyol is often used as the solvent and is combined with a reducing agent and a ligand to prevent NP agglomeration. The polyol method was shown to be very promising for the preparation of uniform NPs with a narrow size distribution for potential use in biomedical applications [65,66]. Figure 7 shows some examples of the polyol method for the preparation of NiCu MNPs.

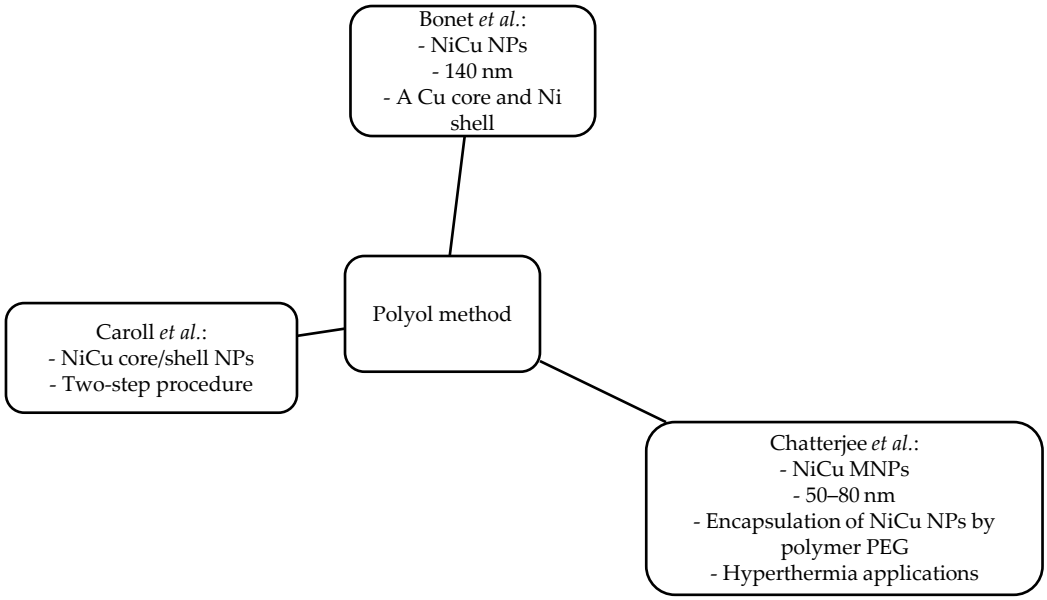

Figure 7. The polyol method as a method for the synthesis of NiCu MNPs. PEG—polyethylene glycol. The references to respective studies mentioned in the figure are as follows: Caroll et al. [67], Bonet et al. [68], and Chatterjee et al. [47].

2.5. Electrochemical Deposition

Electrodeposition of metals and alloys is of wide interest and finds application in a number of fields. The electrodeposition technique involves the use of a conducting surface, onto which metal or alloy sample coatings are deposited using electrolysis. This process is performed using an electrolyte with a strictly defined composition (bath), which can be an aqueous solution of a simple salt, complex salt, or mixture [69]. Figure 8 shows some examples of the electrochemical deposition method for the preparation of NiCu MNPs.

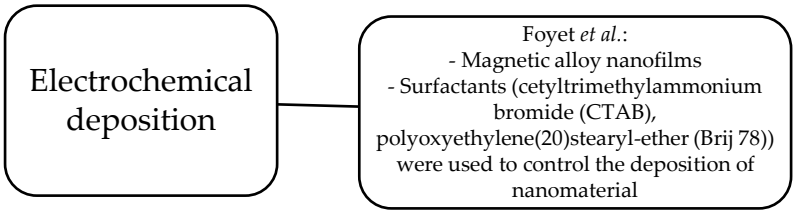

Figure 8. Electrochemical deposition as a method for the synthesis of NiCu MNPs. The reference to the mentioned study is *Foyet* et al. [70].

2.6. Hydrothermal Reduction

Hydrothermal synthesis refers to the synthesis of substances via chemical reactions in a sealed and heated solution above ambient temperature and pressure. The crystal growth is normally performed in an apparatus consisting of a steel pressure vessel called an autoclave. Hydrothermal synthesis involves water acting both as a catalyst and occasionally as a component of solid phases during synthesis at elevated temperature and pressure [71]. Figure 9 shows some examples of hydrothermal reduction for the preparation of NiCu MNPs.

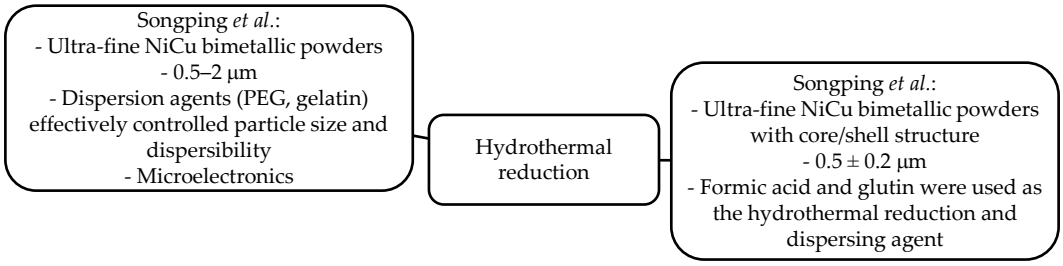

Figure 9. The hydrothermal method as a method for the synthesis of NiCu MNPs. The references to respective studies mentioned in the figure are as follows: Songping et al. [41], and Songping et al. [72].

2.7. Other Methods

MNPs can also be synthesized by other methods, such as hydrogen reduction [21,38], a combination of melting and ball milling [48], hot compressed water [54], electrical explosions [73], pulsed-spray evaporation [74], the solution combustion method [75], the sonoelectrochemical technique [76], solvothermal synthesis from metal precursors [77], and the polymeric precursor method [78]. Figure 10 summarizes some examples of other methods that were reported for the preparation of NiCu MNPs.

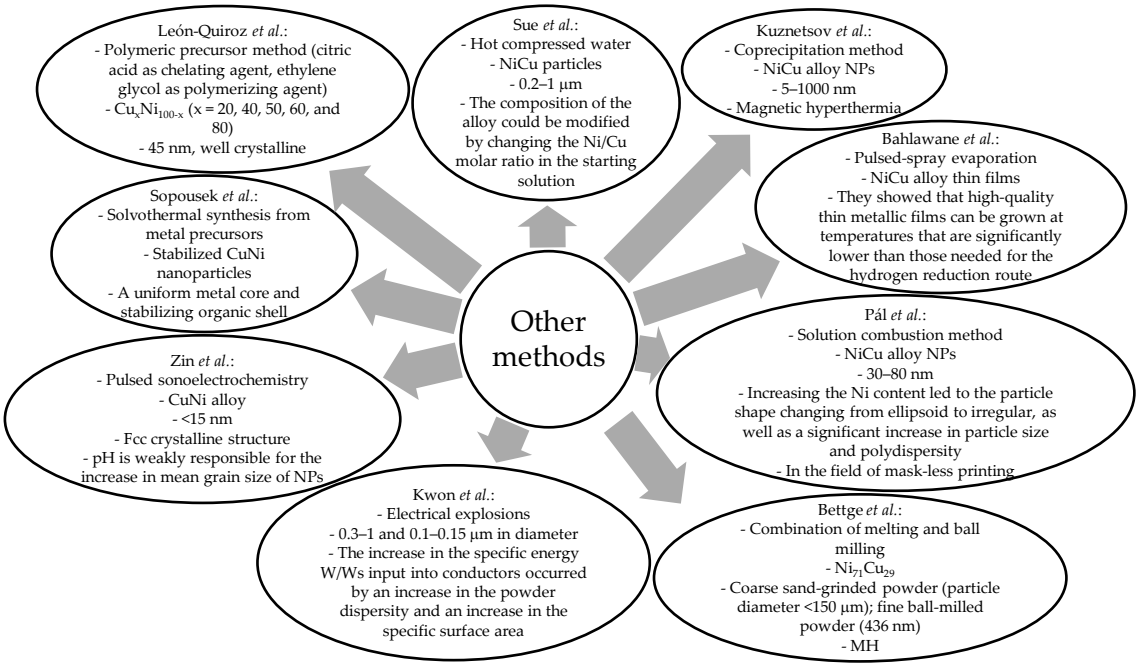

Figure 10. Other methods for the synthesis of NiCu MNPs. Fcc—face-centered cubic. The references to respective studies mentioned in the figure are as follows: León-Quiroz et al. [78], Sopousek et al. [77], Zin et al. [76], Sue et al. [54], Kuznetsov et al. [38], Bahlawane et al. [74], Pál et al. [75], Kwon et al. [73], and Bettge et al. [48].

Figure 11 shows a schematic that depicts the general outlines of the most commonly employed methods to synthesize NiCu MNPs. Furthermore, Figure 12 shows TEM or SEM micrographs of the NPs resulting from most of the mentioned synthesis methods.

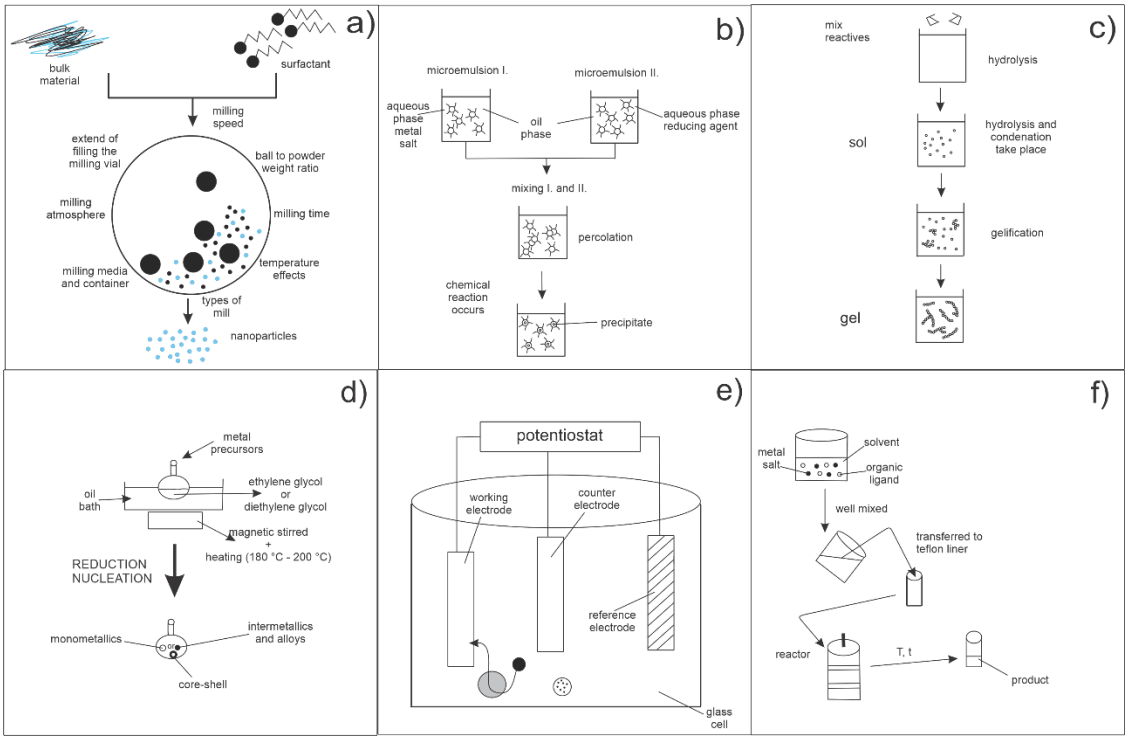

Figure 11. Schematic representation of different synthesis methods of NiCu MNPs: (**a**) mechanical milling, (**b**) microemulsion, (**c**) sol–gel, (**d**) the polyol method, (**e**) electrochemical deposition, and (**f**) hydrothermal reduction.

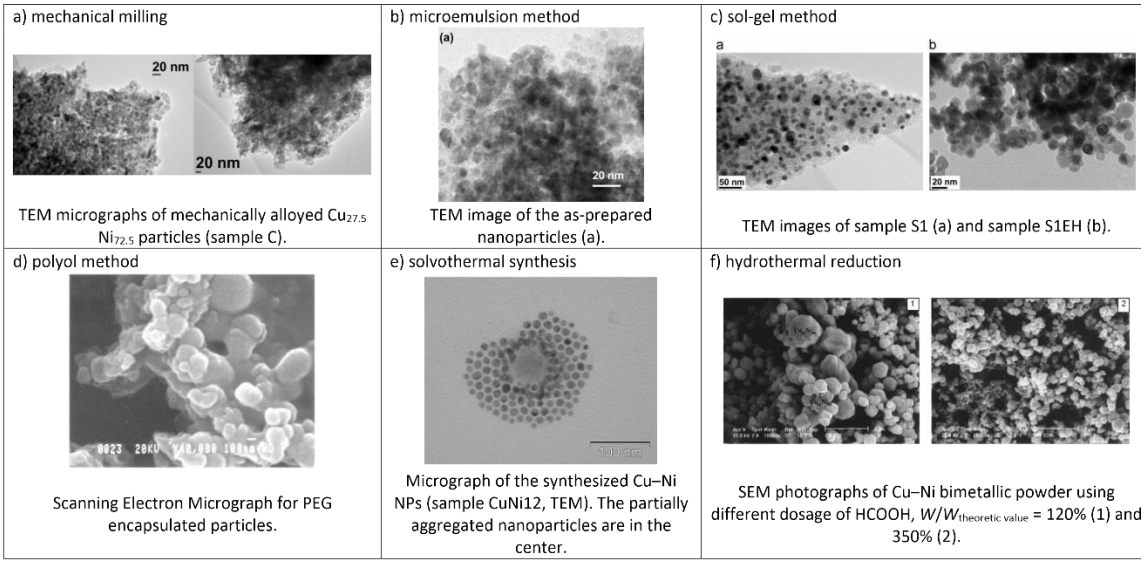

Figure 12. TEM or SEM micrographs of NiCu MNPs prepared using different synthesis methods: (**a**) mechanical milling [36], (**b**) microemulsion [79], (**c**) sol–gel [40], (**d**) the polyol method [47], (**e**) electrochemical deposition [77], and (**f**) hydrothermal reduction [41]. Permission for micrograph reuse was granted by the respective publishers.

In Table 1, we summarize the available preparation methods of different NiCu formulations and their main properties (type, size, structure) and their general usability [80]. Table 1 also compares the different NiCu MNP preparation procedures, with a focus on the general properties of the synthesized NiCu formations, their advantages and disadvantages, and their possible biomedical applications.

Table 1. Preparation methods, types of material, magnetic nanoparticle (MNP) size, advantages and disadvantages, and biomedical applications of different NiCu structures. MH—magnetic hyperthermia.

Method	Types of Material	MNP Size	Advantages	Disadvantages	Biomedical Applications	References
Mechanical milling	- Nanocrystalline Ni_xCu_{1-x} alloys - NiCu nanoparticles	10–436 nm	- A good milling yield (>95%) - Broad NP size distribution - Biocompatibility - T_C = 46–47 °C	- Fe contamination - T_C of 45 °C - Agglomeration - Agglomeration without a liquid medium	- Controlled MH applications	[36,39,48,57]
Microemulsion technique	- NiCu alloy nanoparticles	4–30 nm	- Spherical, uniform NPs - Monodispersed, spherical NPs - Crystallization behavior - Fast synthesis procedure	- A core/shell structure - Additional step (reduction)	- MH	[42,58–61]
Sol–gel method	- NiCu alloy nanoparticles	1–200 nm	- Spherical shape - Narrow NP size distribution, spherical shape	- High dispersion - The silica matrix influences magnetic behavior	- MH	[40,64]
Polyol method	- NiCu magnetic nanoparticles - NiCu core/shell nanoparticles	40–140 nm	- A uniform shape - T_C = ~77 °C - Simple procedure	- A Cu core and a Ni shell - Two-step procedure	- MH	[47,67,68]
Electrochemical deposition	- Magnetic alloy nanofilms	/	- Nanostructured films	- Two peaks in the polarization curve	/	[70]
Hydrothermal technique	- Ultra-fine NiCu bimetallic powders - Ultra-fine NiCu bimetallic powders with a core/shell structure	0.5 ± 0.2 μm	- Excellent dispersibility, a uniform size - Finest dispersibility	- Agglomeration	/	[41,72]
Other methods	- NiCu alloy nanoparticles - NiCu alloy thin films - NiCu alloy NPs	5–1000 nm	- The composition of the alloy could be controlled by changing the Ni/Cu molar ratio in the starting solution - Applying a magnetic field (44 kHz) on the liver resulted in temperature stabilization (42 °C) - Superparamagnetic behavior - Irregular shapes of NPs	- Polydispersed particles - Additional thermal treatment - Heterogeneously distributed particle size - Broad size distribution - Oxidized surface in air	- MH	[38,48,54,73–78]

3. NiCu MNP Functionalization Methods

Most MNPs require modifications to their surface for improved biocompatibility to increase the possibility of their use in biomedicine [81]. The following diverse groups of coating materials were used to modify MNP surface chemistry:

- Synthetic polymers, such as polymethylmethacrylate (PMMA), poly(lactic-*co*-glycolic acid) (PLGA), poly(vinylpyrrolidone) (PVP), polyethylene glycol (PEG), polyvinyl alcohol (PVA), and alginate [81–84];
- Natural polymers, such as dextran, starch, chitosan, pullulan, and gelatin [85–89];
- Organic surfactants, such as dodecylamine, oleic acid, oleylamine, sodium carboxymethylcellulose, and sodium oleate [90,91];
- Inorganic metals (e.g., gold and silica) are the most often used surface functionalization layers of MNPs [90,92];
- Bioactive molecules and structures, such as liposomes, lipids, ligands/receptors, and peptides [93–97].

Some of the abovementioned surface functionalization methods were employed for NiCu MNPs.

Chatterjee et al. [47] prepared PEG-functionalized NiCu MNPs using two different preparation techniques. Ultrasonication was used to prepare a stable and homogenous dispersion of NiCu MNPs in PEG as part of the first method, and an oil (a mixture of n-hexane, mineral oil, and sodium sesquioleate)/water (suspension of NiCu particles in a PEG solution) microemulsion was prepared in the second method. In the second method, ultrasonication was used to homogenize the dispersion, followed by cross-linking. TEM analysis revealed that the first approach formed more composites, while, in the second approach, the encapsulation of spherical NiCu MNPs predominated. The average sizes of the prepared NPs (and composites) were between 200 and 500 nm, and the main factor that influenced their size was the initial NP size. The encapsulated particles had a T_C in the desired range of 320–330 K, which is in the therapeutic range for MH applications. The saturation magnetization for the $Ni_{70}Cu_{30}$ composition was ~6–8 emu/g [47].

Biswas et al. [98] synthesized a NiCu nanoalloy with chain-like particles. Their preparation method was performed using two polymers: PEG and poly(4-vinylphenol) (PVPh). These materials were used to stabilize the structure of the forming nanoalloy and to control the structural features of the forming particles, respectively. Using this method, the authors obtained two types of final products, namely, NiCu–PEG and NiCu–PVPh alloy nanostructures. Simultaneously, they prepared a control NiCu alloy sample without the use of these polymers. The formed products differed in their dispersibility in organic and water-based solvents. For example, the NiCu–PEG particles could be dispersed in both water and (some) organic solvents (dioxan, xylene, acetonitrile, and ethanol). On the contrary, the NiCu–PVPh particles could be dissolved in water and in dimethylformamide (DMF). The authors used TEM analysis to assess the shapes and sizes of the prepared alloy nanostructures. For the NiCu–PEG sample, the images revealed chain-like structures that were formed from apparently spherical NPs with an average diameter of 8 ± 1.1 nm. For the other sample, NiCu–PVPh, similar nanochains were formed with a comparable average size of 7.5 ± 1.8 nm. The saturation magnetization for NiCu–PEG was 38 emu/g; it was 34 emu/g for NiCu–PVPh and 11.5 emu/g for bare CuNi. The presence of copper oxide over bare NiCu (X-ray diffraction (XRD) analysis) was probably the reason that the saturation magnetization value of bare NiCu was lower than that of the other two polymer alloy samples [98].

Araújo-Barbosa et al. [99] produced non-aggregated and monodispersed NiCu alloy NPs embedded in a chitosan matrix. A modified sol–gel method that included the use of the chitosan polymer prevented the particles from aggregating and favored the formation of particles with a narrow size distribution. The mixing step of the synthesis, which involved mixing $Ni(NO_3)_2 \times 6H_2O$ and $CuCl_2 \times 2H_2O$ with a chitosan solution, was performed at room temperature. After 20 min of stirring, they added 1 mL of glutaraldehyde and stirred for an additional 20 min. They let the dispersion rest for 1 h to allow polymerization to occur. After polymerization, they treated the precursor in vacuum at 450 °C for 1.5 h. The second heat treatment was performed in a H_2 gas atmosphere (6 mL/s) for 1.5 h

at 450 °C. They prepared four samples with different compositions: $Ni_{70}Cu_{30}$, $Ni_{75}Cu_{25}$, $Ni_{81}Cu_{19}$, and $Ni_{95}Cu_5$ (all wt.%). The TEM images showed well-dispersed, non-aggregated NPs with specific morphologies. The sizes of the NPs ranged between 11 and 20 nm. Magnetic moments increased (per unit cell) with increasing Ni concentration, and the samples had a specific loss power of up to 5.86 W/g at a low field and frequency, which indicated a promising efficiency for MH [99].

Wen et al. [61] prepared NiCu MNPs by the reduction of $CuSO_4 \times 5H_2O$ and $NiCl_2 \times 6H_2O$ with KBH_4 in a positive (hexane/sodium oleate/water) system and then functionalized their surface using oleic acid directly in the formed microemulsion. The as-synthesized alloy NPs exhibited an amorphous structure and were further annealed at 923 K for 0.5 h in argon to obtain the desired crystal structure. TEM analysis of the as-synthesized NPs showed an average particle size of 4–7 nm, and the particles did not agglomerate. To prevent their agglomeration during annealing, the authors of the study coated them with oleic acid, and they used thermogravimetric analysis to show that oleic acid efficiently covered the particle surface. A weight loss between 572.2 and 651.9 K was reported as a confirmation of the presence of oleic acid in the prepared samples. According to the authors, this weight loss can be attributed to the evaporation and decomposition of oleic acid. Analysis of the magnetic properties of the synthesized MNPs revealed special soft magnetic characteristics [61].

Pramanik et al. [100] prepared NiCu NPs composed of tunable ratios of the respective metals in SiO_2 films. Initially, they formed undoped inorganic-organic hybrid solutions based on tetraethyl orthosilicate (TEOS), 3-(glycidoxypropyl) trimethoxysilane (GLYMO), *n*-butanol, water, methanol, HNO_3, and aluminum acetylacetonate ($Al(acac)_3$) [100]. To perform metal ion doping, the authors prepared five different sols to achieve various Ni/Cu ratios ($Ni_{1-x}Cu_x$; x = 0, 0.333, 0.5, 0.666, 1). The ratio of $Ni_{1-x}Cu_x$ to SiO_2 = 20:80 was kept constant, regardless of the sol composition. The final (control) sol was undoped, and its SiO_2 content was the same as that of the other compositions. The next preparation step was the formation of silica coatings. Using the $Ni_{1-x}Cu_x$ samples, they prepared five different thin film samples and dried them in a two-step process (drying at 60 °C for 1 h, followed by drying at 90 °C for another 1 h). The as-prepared thin film samples were further heat-treated in another two-step procedure (first in air at 450 °C for 1 h and then in a 10 wt.% H_2/90 wt.% Ar atmosphere at 750 °C for 1 h). The first heat treatment step was to remove organics, and the second step was to complete the alloy formation. With the same steps, the control (undoped) NiCu coating was prepared on a polished silicon wafer. The authors then assessed the thicknesses of the prepared thin films. The average thickness was measured to be 310 ± 10 nm. Furthermore, the authors reported that the prepared film sample showed excellent adherence, as well as very good abrasion resistance [100]. From XRD diffractograms, the authors determined that a NiCu face-centered cubic (fcc) alloy was formed with an average size of 6 nm. Finally, the particle size was determined using TEM. The determined values were in agreement with those from the XRD analysis (~6.35 nm). TEM analysis further confirmed that the NiCu NPs were embedded in silica [100].

Stergar and Ferk et al. reported the preparation of NiCu MNPs using an emulsion-based approach [60] and the sol–gel process [37,40]. In both cases, the authors reported the use of silica as the stabilizing component for the prevention of MNP agglomeration. In the emulsion-based approach, they mixed the metal chlorides with hydrazine hydrate and NaOH to form a cationic water-in-oil microemulsion [101]. The silica surface protection layers (10 nm thick) were prepared from a solution of TEOS in ethanol with polyvinylpyrrolidone (PVP) as a surfactant and ultrasonication for 24 h at 60 °C. Apparently, the T_C value was not affected by the coating procedure. The magnetization of the uncoated sample was 22 emu/g, and no hysteresis or superparamagnetic behavior was observed for this sample. On the other hand, the coated particles exhibited 7 emu/g magnetization, as well as marked hysteresis. According to the obtained results, the silica-based coating effectively diminished potential agglomeration during the heat treatment while simultaneously improving the biocompatibility of the MNPs [60]. In the sol–gel process-based method, Ferk et al. also prepared NiCu MNPs, which were stabilized using silica-based functionalization [37,40]. Firstly, the authors prepared a solution of Ni and Cu salts, citric acid, and other components for the synthesis (i.e., deionized water, ethanol, and TEOS).

As in previous studies, the authors followed a multi-step drying/heating regime until the final NiCu MNP product was prepared. The process included a drying step for 72 h at room temperature and two-step calcination of the formed gel in air at 500 °C for 24 h [40] and at 800 °C for 6 h [37]. The final product was a powder mixture of Ni and Cu oxides in a silica matrix. To homogenize the product and form NiCu MNPs in silica, the authors used a H_2/Ar atmosphere. The particles exhibited a narrow particle size distribution with an average diameter of 16.6 nm. The T_C was 63 °C for $Ni_{67.5}Cu_{32.5}$, 54 °C for $Ni_{62.5}Cu_{37.5}$, and 51 °C for $Ni_{60}Cu_{40}$. In this case, the authors showed that, although silica prevented the agglomeration of the formed NiCu MNPs, it also had some negative influences on the samples. In particular, their magnetic and calorimetric properties were decreased. The as-prepared samples (in a silica matrix) were exposed to an etching solution (a mixture of NaOH/hydrazine hydrate) to obtain NiCu MNPs only. For 24 h, the samples were continuously stirred in an Ar atmosphere, after which the NiCu MNPs were collected by centrifugation [37,40].

4. Application of NiCu MNPs in Biomedicine

NiCu MNPs are still considered novel materials that can be produced through environmentally friendly methods and exhibit properties that are appropriate for biomedical use. Despite their relatively recent development, they were the subject of an increasing number of studies over the last few years (Figure 2).

As in the case of other superparamagnetic MNP investigations, most of the NiCu MNP research studies focused on MH applications [36–40,47,48,60,79,99]. In addition to the studies mentioned above, newer studies reported their potential use in bimodal cancer treatment formulations (e.g., a combination of MH and controlled drug delivery) [16], as part of medical implants [49,101], in formulations with antibacterial activity [102], and as part of dental materials [103]. The potential uses of NiCu MNPs in biomedicine are summarized in Figure 13.

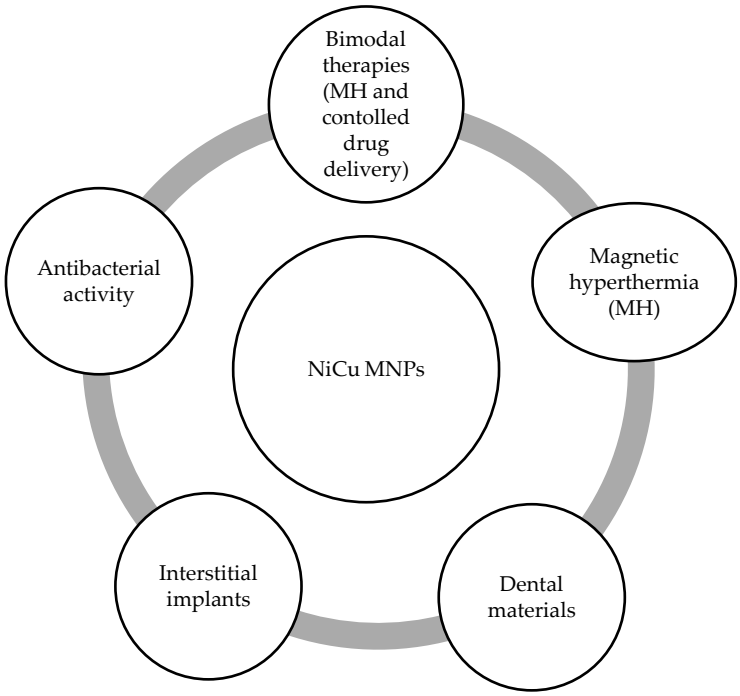

Figure 13. Potential applications of NiCu MNPs in biomedicine. The references to respective studies mentioned in the figure are as follows: Antibacterial activity [60], Bimodal therapies [17], MH [37–41,48,49,96,98,99], Interstitial implants [50,100], Dental materials [101].

Because of the steadily increasing number of research studies on NiCu-based materials for these and other types of applications, this section reviews their different uses, with an explicit focus on synthesis, functionalization, and other aspects that make them appropriate for biomedical purposes.

4.1. Magnetic Hyperthermia

MH is a promising non-invasive type of cancer therapy that makes use of MNPs that generate heat under controllable external stimuli. It uses a combination of an AMF and biocompatible MNPs with a T_C value as close as possible to 42–46 °C as heating agents. This temperature interval was proven to be ideal for destroying cancer cells with minimal harm to the healthy surrounding tissues [17]. Therefore, it is important to understand the underlying physical mechanisms via which heat is generated in small MNPs by AMFs [104]. Among the various available MNPs, NiCu MNPs with a tailorable T_C in the temperature interval 42–46 °C seem ideally suited for future effective MH formulations [36,38,39,47,48].

Bettge et al. [48] developed a new, relatively simple procedure for NiCu alloy particle synthesis that was based on the combination of ball milling and the melting of bulk materials. The resulting formulation consisted of particles with sizes below a micron that were shown to be good candidate materials for self-controlled MH treatment. The milled particles were found to be slightly above 400 nm. However, their most important finding was that the prepared formulation exhibited a T_C in the desired therapeutic range (46–47 °C), making them suitable for self-regulating MH. Using TEM analysis, the authors further determined that the particles were not uniform in shape, with some of them being spherical and the others having a flake-like appearance [48].

Chatterjee et al. [47] prepared novel NiCu NPs with a PEG surface layer using the polyol reduction technique. In addition to the other advantages of the PEG coating (e.g., decreased agglomeration, improved biocompatibility), a beneficial effect was observed on the T_C, which fell from ~77 °C to the desired ~46 °C. Furthermore, the coated NPs showed a suitable saturation magnetization of 6–8 emu/g. These findings all suggest that the prepared PEG-functionalized NPs are promising materials for use in MH [47].

Kuznetsov et al. [38] produced alloy NiCu MNPs using various methods. The authors reported that the best results were obtained by the co-precipitation of Cu and Ni salts in the presence of Na_2CO_3 at room temperature, with a consecutive reduction in a H_2 atmosphere (at 300–1000 °C). This initial particle preparation step was followed by various grinding/separation methods to achieve more uniform NP sizes, as well as a more homogenous composition. This step also enabled the control of the formulation's T_C and, thus, increased their potential for use in MH. The potential applicability of the prepared materials to cancer treatment was shown by testing this formulation on a rat liver tumor model. The results showed their effective potential use as part of magnetic fluid hyperthermia [38].

Ban et al. [36] showed the potential of a simple milling-based method to produce nanosized NiCu alloy NPs with potential application in MH. By optimizing the milling process, they were able to produce nanocrystalline $Ni_{72.5}Cu_{27.5}$ alloy NPs with an average size of 10 nm. Further, the particles exhibited a T_C in the MH suitable therapeutic range (~45 °C). The authors proved the superparamagnetic nature of the prepared NiCu NPs by showing that the hysteresis loops lacked remanent magnetization. Significant heat induction of the powdered samples indicated that they are highly promising for use in self-regulating MH [36].

Stergar et al. [101] reported another interesting synthesis approach to preparing Ni_xCu_{1-x} NPs in a water/oil (W/O) microemulsion. Although the particles were partially agglomerated (confirmed using TEM analysis), they exhibited an average size of ~30 nm. The most likely explanation for the determined T_C being very close to that of pure Ni was that the particles showed a core/shell structure. To homogenize the sample, the authors performed a heating step in a reducing atmosphere in a tube furnace at 900 °C. This led to the formation of a solid solution of Ni/Cu, which had an expected *T*c value of ~65 °C according to the formulation's nominal composition. Again, a silica coating proved to be the right choice to prevent particle agglomeration without affecting the T_C value [60]. Although the developed synthesis method is very promising for the preparation of a versatile range of NiCu MNPs, the authors noted that further optimizations of the formulation are necessary to achieve a *T*c in a range that is suitable for use in MH.

Ferk et al. [40] developed a sol–gel-based NiCu MNP preparation method, which yielded NPs with a narrow size distribution. The method included the reduction of Ni and Cu oxides in silica, leading to the formation of Ni_{1-x} Cu_x MNPs in SiO_2. To obtain pure particles, the authors etched the silica matrix using NaOH/hydrazine hydrate. Through this processing, only $Ni_{67.5}Cu_{32.5}$ nanospheres with a narrow size distribution were retained in the sample. Thermogravimetric analysis (TGA)/single differential thermal analysis (SDTA) was used to determine a T_C value of ~65 °C for the samples [40]. This was the first study to report the successful production of superparamagnetic NiCu nanospheres with a narrow size distribution and the capability of controlling the T_C for potential application in MH [40].

Amrollahi et al. [39] used mechanical milling to produce $Ni_{0.5}Cu_{0.5}$ NPs for potential use in MH applications. The ball milling-based initial synthesis stage (30 h) was concluded with a heating step for 1 h at 500 °C. Using XRD analysis, the authors showed that only single-phase NPs were formed. The particle size and rate of agglomeration were established using TEM. The authors reported a narrow size distribution of particles with an average size of ~20 nm, although these were mostly part of larger agglomerates. Nevertheless, the potential of the prepared NPs for use in MH was proven by their measured T_C of 44 °C. To further demonstrate the suitability of these NPs for MH, the authors performed biocompatibility/cytotoxicity testing using human bone marrow stem cells (hMSCs) and proved that the formulation did not harm them [39]. A summary of various other related research studies that reported the use of NiCu MNPs in MH (including some of their most important properties) is shown in Table 2.

Table 2. Type, synthesis method, composition (w), average particle size (d_x), Curie temperature (T_C), magnetization (Ms), and specific absorption rate (SAR) of NiCu materials for MH. PEG—polyethylene glycol.

Types of Materials	Synthesis Methods	Surface Modification	w (atm. %)	d_x (nm)	T_C (°C)	M_S (emu/g)	SAR (W/g)	References
CuNi alloy NPs	Polyol reduction method ——-and——— physical melting process	PEG	$Cu_{30}Ni_{70}$	50–80 ——— 300–400	43–46	45 ——————- 6–8	/	Chatterjee et al. [47]
NiCu alloy NPs	Sol–gel method	Silica matrix	$Ni_{67.5}Cu_{32.5}$ $Ni_{62.5}Cu_{37.5}$	15–20	51–63	3–9	0.12–0.60	Ferk et al. [37]
NiCu alloy NPs	Sol–gel method	Silica matrix	$Ni_{60}Cu_{40}$ $Ni_{67.5}Cu_{32.5}$	16	65	8	/	Ferk et al. [40]
$Cu_{1-x}Ni_x$ NPs	Cationic water-in-oil (W/O) microemulsions	Silica	$Ni_{70}Cu_{30}$ $Ni_{72.5}Cu_{27.5}$ $Ni_{60}Cu_{40}$	/	45–88	22 (uncoated) 7 (coated)	/	Stergar et al. [60]
$Ni_{1-x}Cu_x$ alloys	Modified sol–gel method	Chitosan matrix	$Ni_{70}Cu_{30}$ $Ni_{75}Cu_{25}$ $Ni_{81}Cu_{19}$	11–20	77–277	21–50	0.289–0.576	Araújo-Barbosa et al. [99]
CuNi NPs	Mechano-thermal method	/	$Ni_{95}Cu_5$ $Cu_{50}Ni_{50}$	20	44	18	260.44	Amrollahi et al. [39]
CuNi alloy NPs	Co-precipitation of salts from solution followed by reduction in hydrogen and thermal treatment (sol–gel method)	NaCl matrix	25–30 atm.% of Cu	30	40–60	/	/	Kuznetsov et al. [38]
NiCu NPs	Melting and ball milling	/	$Ni_{70}Cu_{30}$ $Cu_{40}Ni_{60}$	436	46–47	/	/	Bettge et al. [48]
Cu_xNi_{1-x} alloys	Mechanical milling	/	$Cu_{30}Ni_{70}$ $Cu_{27.5}Ni_{72.5}$ $Cu_{27}Ni_{73}$ $Cu_{25}Ni_{75}$	10–12	24–174	4.4–32.9	/	Ban et al. [36]
CuNi alloy NPs	Microemulsion method	/	$Cu_{20}Ni_{80}$ $Cu_{27.5}Ni_{72.5}$	28	43	2.5–20	4.3–41.6	Stergar et al. [79]

4.2. Bimodal Cancer Therapy (A Combination of MH and Controlled Drug Delivery)

Controlled drug delivery systems have several advantages compared with traditional pharmaceutical formulations. For example, they enable drug transportation to the desired site of action in the body with minimal damage to healthy surrounding tissues. Delivery systems with these characteristics are key for drugs that exhibit a narrow therapeutic index or drugs that are directly cytotoxic to healthy cells (e.g., most antitumor drugs) [17]. Recent findings suggest that NiCu MNPs are very promising for the combination of MH and controlled drug delivery [17].

Stergar et al. [16] prepared a novel controlled drug delivery formulation composed of $Ni_{67.5}Cu_{32.5}$ MNPs in a silica matrix synthesized using the sol–gel procedure. They used the fluorescent dye rhodamine 6G to evaluate the ability of MNPs to deliver the drug to various human cells (a healthy cell line of human skin-derived fibroblasts and the cancerous cell lines HeLa and Caco-2). The progressive $Ni_{67.5}Cu_{32.5}$ MNPs were shown to be a dependable (confirmed through biocompatibility and cytotoxicity assays) and efficient delivery system (in vitro cell delivery model) to various human cell types. The obtained results indicate that the proposed formulation has a very high potential for the future development of drug delivery systems that specifically target these cells. The process explored the protection of particles during drug delivery and MH, and the results confirmed the successful application of $Ni_{67.5}Cu_{32.5}$ particles with a T_C of about 43 °C and drug accumulation in a silica protecting layer.

4.3. MH Implants

Interstitial hyperthermia using magnetic materials is known as magnetic induction hyperthermia. Soft heating or implant heating systems are excellent systems for this purpose. In these systems, the ferromagnetic material (implant) is firstly implanted in the cancer tissue, followed by the utilization of an eddy current or magnetic hysteresis loss under a high-frequency AMF to generate highly localized heating. The temperature of the cancer tissue is raised and regulated at the T_C of the implant material [105].

Paulus et al. [49] explored novel, low-*T*c ferromagnetic NiCu (28 wt.% Ni) and PdCo (6.15 wt.% Pd) formulations as part of interstitial implants in prostate cancer therapy. Initially, they performed a melting step, in which both alloys were put into a carbon arc furnace. This step was followed by a heat treatment step to induce sample recrystallization (at 1000 °C). The annealed NiCu and PdCo samples were spot-welded to Cu wire connections, and the junctions were closed using a water-resistant epoxy adhesive. Potential contaminants on the sample surface were removed by polishing using a 1-µm diamond paste. The as-prepared samples proved to be more corrosion-resistant, even after longer immersion times. The authors explained this phenomenon by the formation of passivation layers on the sample surface. It was further established that the PdCo alloy outperformed the NiCu sample with regard to the corrosion stabilization time in solution. This finding was additionally backed by proving the excellent corrosion resistance of this sample in vitro. On the basis of all the findings, the authors concluded that the developed formulations are promising for the intended use, even in long-term hyperthermia applications [49].

El-Sayed et al. [101] developed a manufacturing procedure of PdNi, PdCo, and NiCu ferromagnetic thermoseeds to increase the sharpness of T_C for interstitial hyperthermia in cancer treatment. They characterized the prepared seeds by magnetic measurements as a function of temperature and magnetic field strength. The ferromagnetic thermoseeds showed a sharp decrease in ferromagnetic to paramagnetic transition temperatures at 52, 57, and 49 °C and the heat production of T_C. These seeds provided a power output at 20 °C of about 150, 200, and 75 mW/cm, as measured from the hysteresis loops. The temperature dependence of the seed power was computed from a combination of Curie and induction laws. Their computations showed a good agreement with the values calculated from the area under the hysteresis loops at an AMF with a frequency of 100 kHz and field strength of 4 kA/m. The power automatically stopped when T_C was reached, indicating that the seeds had

self-limiting temperature control. This self-limitation indicates the high potential of these seeds for potential exploitation in clinics, especially for treating localized tumors [102].

4.4. Antibacterial Activity

Antibacterial activity is related to compounds that locally kill bacteria or slow their growth without being toxic to the surrounding tissue. In general, the agents can be classified as either bactericidal (agents that kill bacteria) or bacteriostatic (agents that slow bacterial growth) [106]. In the area of antibacterial agents, metal nanoparticles are of particular interest because of their high surface areas and, hence, their large number of potential active (antibacterial) sites per unit area. A distinct class of metal oxides with distinctive magnetic properties and superior biocompatibility is iron-oxide NPs [107]. Indeed, various metal NPs demonstrated broad-spectrum antibacterial properties against both Gram-positive and Gram-negative bacteria. For example, ZnO NPs were found to inhibit *Staphylococcus aureus*, and Ag NPs exhibited concentration-dependent antimicrobial activity against *Escherichia coli* and *Pseudomonas aeruginosa* [106–109]. NiCu MNPs were also previously studied for the same purpose. The example below shows their potential uses for this purpose.

Parimaladevi et al. [102] synthesized Cu, Ni, and CuNi bimetallic NPs through the solvothermal method. They added $CuSO_4$ and NaOH, $NiNO_3$ and NaOH, and $CuSO_4$ and $NiNO_3$ (1:1) to hydrazine (reducing agent) and ethylene glycol (solvent). The mixture was stirred for 15 min and transferred to an autoclave (150 °C, 5 h). The obtained precipitate was separated by centrifugation and washed repeatedly with water and ethanol. The antibacterial activity of Cu, Ni, and CuNi NPs was evaluated against Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli* using a standard agar well diffusion method. A standard antibacterial drug, cefixime, was used in each plate. The test results against the Gram-positive bacterium *S. aureus* showed a higher inhibition compared with the results against Gram-negative *E. coli* for all NPs. Larger zones of inhibition were recorded for CuNi NPs than the monometallic NPs; this observation is most likely the result of the unique distribution of the two different metals, enabling the simultaneous release (and activity) of two different metal ions, namely, Cu^{2+} and Ni^{2+}. The observed toxicity was similar to that of cefixime, suggesting that the CuNi NPs were utilized in abundance at sites of possible infections, such as pneumonia and strep throat. The cost-effectiveness of CuNi NPs and their lethality toward both Gram-positive and Gram-negative bacteria may lead to numerous applications, such as antibacterial coatings, paints, surfaces, and films [102].

4.5. Dental Materials

There are various applications of NPs (carbon-based nanomaterials, hydroxyapatite, iron oxide, zirconia, silica, silver, and titania) in dentistry [110]. Biocomposite materials (e.g., tiny calcium phosphate crystallites) that bear structural and chemical similarity to hydroxyapatite were shown to effectively integrate into growing human bone. This is related to the fact that hydroxyapatite is a natural nanocomposite in the body that is formed naturally by bone-derived cells. Typically, these materials are used as part of implant coatings to improve the implant's overall biocompatibility and often contribute to better wear resistance; both of these functions are important in the preparation of bone grafts. Recently, novel methods in dentistry were developed in which organically modified ceramic and its fillers are used to enhance dispersion and biocompatibility, accompanied by a simultaneous increase in the toughness of the implant. Iron-oxide nanoparticles are very useful for eradicating biofilms on dental implants. Alumina/zirconia nanocomposites are new implant materials that show better efficacy compared with ceramic materials. Zirconia-oxide nanoparticles were found to have anti-biofilm activity against certain bacteria (such as *Enterococcus faecalis*); therefore, they can be used effectively as polishing agents in dental practices [110,111]. NiCu MNPs are also emerging as potential materials for future use in dentistry. Some examples are described below.

Argueta-Figueroa et al. [103] developed various single-metal and bimetallic alloy materials based on Ni and Cu and tested their antibacterial activity. The main purpose of their study was to evaluate

the formulation for use in dentistry. The bimetallic NiCu MNP formulation was prepared by chemical reduction with $NaBH_4$. Antibacterial activity was assessed against three different bacteria, namely, Gram-positive *Staphylococcus aureus*, Gram-negative *Escherichia coli*, and the more dentistry-specific pathogen *Streptococcus mutans* (Gram-positive). Using the developed preparation method for the NiCu MNPs, the authors obtained a combination of three crystal structures, namely, both metal oxides and the alloy (determined through XRD analysis). Of all the synthesis parameters, pH had one of the strongest influences on the final ratio between the metals in the samples. A narrow size distribution and an average size of around 25 nm were found. The as-prepared Cu NPs showed a bactericidal effect on all three tested bacteria, whereas the Ni NPs and the bimetallic NiCu NPs were only bacteriostatic. From the obtained results, the authors concluded that the prepared materials have great potential for future use in dentistry [103].

5. Biosafety Considerations

As is the case with all other formulations for human use, NiCu MNPs must be appropriately evaluated for their safety. This is the most important evaluation since both metal elements can have toxic effects on the human body [112]. Nevertheless, as we showed in one of our previous (in vitro) studies [16], the biocompatibility of $Ni_{67.5}Cu_{32.5}$ MNPs in a silica matrix should not pose a problem. For the time span of the performed study, we are also positive that no leaching of metal ions occurred, which might have negatively affected cell growth [16]. As an integral part of this review, we also present various strategies of NiCu MNP functionalization. The purpose of functionalization is often to improve the biocompatibility of the core materials with the target (human body) environment. Of the most frequently used "shells", silica is by far the most common [90,92]. Therefore, the developed MNPs have very high potential for the future development of drug delivery systems for specific applications targeting cells (and, hence, tissues). Since the core nanoalloy compositions also vary, it is also important to consider Ni/Cu ratios. For example, MNPs with the composition $Cu_{0.5}Ni_{0.5}$ were demonstrated to be safe for cancer treatment applications [39].

Although we understand that further studies are necessary to prove the "full" safety of NiCu MNPs for potential patients, we also acknowledge that there are already available strategies that can diminish even potential toxic effects (the bar for potential risks posed by chemotherapy agents is set relatively low) that might occur with Ni or Cu degradation products [113]. One strategy could be to take advantage of their superior magnetic properties to achieve MH with low MNP concentrations, which are non-toxic. Alternatively, as shown in Section 3, a core/shell strategy to mitigate toxicity can significantly increase the safety of the core material.

6. Conclusions

The presented review summarizes the most important aspects of the preparation of NiCu MNPs with regard to their potential use in biomedicine. This includes different possible synthesis procedures, as well as the necessary functionalization/modification steps that need to be taken to either boost their biocompatibility or prevent agglomeration, which are both factors that contribute to their improved properties for application. As can be concluded from the currently available literature, which grew for the last couple of years, NiCu MNPs could be among future formulations for use as MH formulations, drug delivery systems, or other applications. With an already proven track record of successful application (currently only in in vitro and animal models), the potential of NiCu MNPs will only grow; many research groups are now testing their suitability using various additional tissue models to determine their application as part of the abovementioned uses or even in regenerative medicine, which was not addressed above [114].

Nevertheless, NiCu MNPs do not come without hurdles. Future challenges in their development certainly include the optimization of their synthesis and functionalization, which need to be green, to yield uniform small-sized nanoparticles with a narrow size distribution that are less prone to agglomeration. Additionally, careful composition control is necessary to prepare NiCu MNPs with a

T_C in the therapeutic range to minimize potential damage to healthy tissues. By meeting all of these criteria, their potential in biomedical applications will almost be without limitations, either as part of formulations for "traditional" applications of magnetic materials (e.g., MH) or as part of novel multi-modal drug delivery systems or dentistry implants that exhibit antibacterial activity.

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