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Role of Magnetic Anisotropy on the Hyperthermia Efficiency in Spherical $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) Nanoparticles

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Abstract: The use of magnetic nanoparticles in the treatment of cancer using alternating current hyperthermia therapy has shown the potential to replace or supplement conventional cancer treatments, radiotherapy and chemotherapy, which have severe side effects. Though the nearly spherical sub-10 nm iron oxide nanoparticles have their approval from the US Food and Drug Administration, their low heating efficiency and removal from the body after hyperthermia treatment raises serious concerns. The majority of magnetic hyperthermia research is working to create nanomaterials with improved heating efficiency and long blood circulation time. Here, we have demonstrated a simple strategy to enhance the heating efficiency of sub-10 nm Fe_3O_4 nanoparticles through the replacement of Fe^{+2} ions with Co^{+2} ions. Magnetic and hyperthermia experiments on the 7 nm $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles showed that the blocking temperature, the coercivity at 10 K, and the specific absorption rate followed a similar trend with a maximum at $x = 0.75$, which is in corroboration with the theoretical prediction. Our study revealed that the heating efficiency of the $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles varies not just with the size and saturation magnetization but also with the magnetocrystalline anisotropy of the particles.

Keywords: hyperthermia; magnetic anisotropy; nanoparticles; magneocrystalline; heating efficiency; iron oxide

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1. Introduction

Functional magnetic nanostructures are of high significance not only for research professionals working in the disciplines of data storage [1], catalysis [2,3], environmental remediation [4], and basic science [5–8] but also for those working in biomedicine [9–13]. Recently, alternating current (AC) hyperthermia therapy using magnetic nanoparticles, especially spinal ferrites (MFe_2O_4 , $\text{M} = \text{Mn, Ni, Co, Fe}$), has become a promising supplementary technique to conventional cancer treatments, radiotherapy and chemotherapy, which have severe side effects [14–17]. In the treatment involving magnetic hyperthermia, an external AC magnetic field is applied for heating the magnetic nanoparticles in a cancerous area in order to destroy or deactivate the cancerous cells and cause no harm to the healthy ones, resulting in minimum collateral damage. This technique has already shown promising results in cancer therapy; however, the low heating efficiency of the traditionally used spherical iron oxides, particularly magnetite (Fe_3O_4) and maghemite ($\gamma\text{-Fe}_2\text{O}_3$) nanoparticles, obstructs their wide application [18,19]. Serious concern has been raised about the number of nanoparticles required for each magnetic hyperthermia treatment because of their low heating efficiency. Recent research has suggested that a significant number of nanoparticles tends to be cumulated in kidneys, liver, spleen, and other parts of the body after hyperthermia treatment [20]. Therefore, there is an increase in demand for

highly efficient magnetic nanoparticles so that a minimal dose of nanoparticles can be used to achieve the therapeutic temperature range (40–44 °C) to kill or deactivate the cancerous cells without damaging the healthy ones [21–26].

The heating efficiency of the nanoparticles defined in terms of the specific absorption rate (SAR) value is dependent on the saturation magnetization (M_S), effective magnetic anisotropy, shape, size and amount of the nanoparticles [27–31]. Smaller nanoparticles, in the sub-10 nm range, have been proven to have a longer circulation time in blood because they can escape the immune system. Moreover, smaller nanoparticles are stable against agglomeration and precipitation, thus avoiding the risk of blood vessel occlusion [32]. However, there is a strong decrease in M_S , well below the M_S of bulk phase, upon reduction in the size [33]. Both Monte Carlo simulation and experimental results on Fe_3O_4 nanocubes showed a SAR improvement relative to conventional spherical nanoparticles, due to the enhanced surface anisotropy as a result of the chain-like particle formation [34]. This was further verified by our group, where we have demonstrated a significant enhancement in the SAR value of Fe_3O_4 nanorods compared to other shapes due to enhanced effective magnetic anisotropy [35,36]. Unfortunately, only nearly spherical iron oxide nanoparticles are currently approved for biomedical applications [37–39]. Therefore, a robust strategy is needed to improve the heating efficiency of sub-10 nm iron oxide particles. It has been demonstrated that the heating efficiency of Fe_3O_4 nanocubes (20 ± 2 nm) can be improved with a small replacement of Fe^{+2} with Co^{+2} ions in B-sites, as a result of the increased magnetocrystalline anisotropy in $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ nanoparticles [40].

Even though there is a great potential of Co substituted $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ nanoparticles in improving heating efficiency, the systematical study of sub-10 nm $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles [32,41] has attracted much less research effort. This restrains the possibility of using $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles for magnetic hyperthermia treatment. To address this challenging issue, we fabricated a 7 nm series of $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles, while keeping the size and morphology unchanged. Here, we demonstrate that the magnetocrystalline anisotropy and SAR for these $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles follow a similar trend with a maximum at $x = 0.75$.

2. Materials and Methods

2.1. Synthesis of $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) Nanoparticles

$\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles were fabricated using thermal decomposition of iron acetylacetonate ($\text{Fe}(\text{acac})_3$, Sigma-Aldrich 97%, St. Louis, MO, USA) and cobalt acetylacetonate ($\text{Co}(\text{acac})_2$, Sigma-Aldrich 97%) [42–45]. In a typical reaction, the stoichiometric amount of $\text{Fe}(\text{acac})_3$ or/and $\text{Co}(\text{acac})_2$ (2 mmol) and 1,2 hexadecanediol (Sigma-Aldrich 90%) (10 mmol) were dissolved in 6 mmol of oleic acid (Sigma-Aldrich 90%), 6 mmol of oleylamine (Sigma-Aldrich 70%) and 20 mL of benzyl ether (Sigma-Aldrich 98%). For nucleation of the particles, the mixture was stirred in a nitrogen atmosphere while being heated to 200 °C and was kept constant for 2 h, following which it was raised to 280 °C for the growth process. The temperature was kept constant at 280 °C for 1 h, and then the reaction mixture was naturally cooled to ambient temperature (300 K). The resultant $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles were washed with ethanol and hexane (3:1) three times. The stoichiometry of the $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles was controlled by choosing the appropriate initial ratio of precursors, $\text{Fe}(\text{acac})_3$ and $\text{Co}(\text{acac})_2$. The experimental conditions for every reaction were kept constant to obtain the same size and morphology of the $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles. After washing, the black precipitates were re-dispersed in hexane for storing and further characterization.

2.2. Phase Transfer of $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) Nanoparticles

The as-prepared oleic acid and oleylamine capped hydrophobic nanoparticles were phase transferred to the aqueous phase using tetramethyl ammonium hydroxide (TMAH) (Sigma-Aldrich $\geq 97\%$) as a capping agent [32]. The as-prepared nanoparticles were dried by air. For a standard reaction, 100 mg of dried $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles was

dispersed in a solution containing 500 mg of TMAH in 10 mL of ethanol. For all the phase transfer processes, the ratio of nanoparticles:ethanol:TMAH was kept at 1:10:5. The above mixture was sonicated for 30 min and then washed with water to get rid of extra TMAH. The washed particles were dispersed in water for the hyperthermia measurements. The TEM images of the nanoparticles exhibited no indication of particle size and morphology change due to the phase transfer from the hydrophobic to the aqueous medium [35].

2.3. Characterization of the Nanoparticles

Crystalline phase and morphology were characterized using a Bruker AXS D8 X-ray Diffractometer (XRD) (Bruker, Madison, WI, USA) and a FEI Morgagni 268 Transmission Electron Microscope (TEM) (FEI, Hillsboro, OR, USA) operating at 60 kV, respectively. DC magnetic measurements were done using a vibrating sample magnetometer (VSM) of Physical Property Measurement System (PPMS) from Quantum Design, San Diego, CA, USA. Calorimetric hyperthermia experiments were conducted using a 4.2 kW Ambrell Easyheat Li3542 system (Ambrell, Rochester, NY, USA) with AC fields (0–800 Oe) and frequency ($f = 310$ kHz).

3. Results

Thermal decomposition of $\text{Fe}(\text{acac})_3$ and $\text{Co}(\text{acac})_2$ was used to synthesize spherical $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles; the specifics are mentioned in the Materials and Methods section. In the thermal decomposition reaction, the decomposition of $\text{Fe}(\text{acac})_3$ and $\text{Co}(\text{acac})_2$, in the presence of 1,2 hexadecanediol, oleic acid, and oleylamine, to cationic metals resulted in the formation of the nanoparticle. In the current case, at 200 °C, the nucleation process occurred, followed by the growth of the nucleus at 280 °C. The segregation of nucleation and the growth process directed the formation of the monodisperse nanoparticles [42,43]. The size and morphology of the particles are dependent on the initial ratio of the precursors, surfactants and solvent.

TEM images of $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles are displayed in Figure 1. The analysis of the TEM images shows that along with having a nearly monodisperse size distribution, the particles are nearly spherical in shape. It is worth mentioning that the particles are well separated from each other, which indicates the uniform surfactant coating of the nanoparticles' surface. The mean diameter (D) and a standard deviation (σ) from the fitting of the size histogram to a lognormal distribution are presented in Table 1. The mean diameter of the particles for all compositions is in the range of 6.6 to 7.8 nm. This control over the size of $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles allowed us to understand the effect of Co substitution on their magnetic and hyperthermia responses.

Figure 1. TEM images of $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ nanoparticles with cobalt content of (a) $x = 0$, (b) $x = 0.07$, (c) $x = 0.10$, (d) $x = 0.50$, (e) $x = 0.75$, and (f) $x = 1$. The inset of each image shows the corresponding diameter histograms. Scale bar is 20 nm in all the images.

Table 1. Size of nanoparticles corresponding to the Co content in $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$).

$\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ (x)	Mean Diameter (D) in nm	Standard Deviation (σ) in nm
0	7.8	0.1
0.07	6.7	0.1
0.10	6.6	0.1
0.50	7.2	0.4
0.75	7.1	0.2
1	6.5	0.1

The crystalline phase of the $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles was analyzed using XRD. In the XRD pattern of $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0.10$) displayed in Figure 2, the XRD peaks are indexed to Fe_3O_4 confirming the formation of the single-phase material. The formation of the single-phase material confirms that the oleic acid and oylamine capping inhibits the oxidation of the nanoparticles.

Figure 2. XRD pattern of $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0.10$) nanoparticles. The lower pattern corresponds to the standard cubic Fe_3O_4 .

Zero-field-cooled (ZFC) and field-cooled (FC) magnetization vs. temperature in an applied field of 50 Oe for $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles is shown in Figure 3a. Monodisperse, non-interacting, and superparamagnetic nanoparticles, which are ferromagnetic in the ground state, are known to show a maximum in the ZFC magnetization curve corresponding to the blocking temperature (T_B) when the thermal energy is equivalent to the activation energy. The ZFC magnetization ($M_{\text{ZFC}}(T)$) curves for all the samples clearly showed maxima in the measured temperature range. It is evident that the $M_{\text{ZFC}}(T)$ peak or the T_B shifts to a higher temperature with an increase in the Co content. T_B vs. Co content is plotted in Figure 3b and Table 2. The sharp increase in T_B , with an increase in Co content until $x = 0.75$, can be attributed to the increase in the magnetocrystalline anisotropy of the nanocrystals [37]. The nearly constant value of T_B from $x = 0.75$ to $x = 1$ indicates that the magnetocrystalline anisotropy of the nanocrystals does not increase with a further increase in Co content. This is in agreement with previous reports, where a decrease in magnetocrystalline anisotropy in $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($0.75 \leq x \leq 1$) was reported [40,46–49].

Figure 3. (a) Zero-field-cooling (ZFC) and field-cooling (FC) magnetization curve of 7 nm series of $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles under 50 Oe magnetic field. (b) The Co content dependence of blocking temperatures of $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles.

Table 2. Parameters corresponding to the Co content in $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$).

$\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ (x)	Blocking Temperature T_B (K)	Anisotropy Energy $E_U = T_B \times K_B$ (eV)	Saturation Magnetization M_S at 300 K (emu/g)	Coercivity H_C at 10 K (Oe)	SAR at 800 Oe (W/g)
0	53	0.0045	58.0	330	5 ± 4
0.07	57	0.0049	54.3	1265	12 ± 5
0.10	75	0.0065	54.0	2230	26 ± 3
0.50	157	0.0135	57.5	8126	29 ± 3
0.75	215	0.0185	60.6	17161	38 ± 2
1	218	0.0187	60.7	7649	21 ± 4

To further verify the variation of magnetocrystalline anisotropy in $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles, we measured low temperature (10 K) magnetization as a function magnetic field (M–H) loops (Figure 4a). At 10 K, $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0$) nanoparticles show coercivity of 330 Oe which increases to 1265 with Co content of $x = 0.07$ and show a further increase with an increase in the Co content (Table 2). The variation of H_C at 10 K as a function of Co content ($x = 0-1$) is shown in Figure 4b and Table 2. The H_C at 10 K increases with an increase in the Co content until $x = 0.75$ and above, at which point it showed a decreasing trend. Sathya et al. reported that in the series of 20 nm $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ nanocrystals ($0.1 \leq x \leq 1$), with the increase in cobalt content from 0.1 to 0.5, the H_C at 5 and 298 K increased; additionally, with a further increase to 1, H_C showed a decreasing trend. Yu et al. also observed similar results for 35 nm $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles where the maximum in the H_C was observed at $x = 0.6$, which then decreased with a further increase of Co content [50]. These results convey that the size and crystallinity of the nanoparticles determine the maximum of the H_C with Co content in $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ nanocrystals ($x = 0-1$). This is in corroboration with previous experimental and theoretical results [40,46–49]. It should be noted that although high magnetic anisotropy results in high coercivity, high coercivity does not always mean high magnetic anisotropy as there could be other factors that can account for magnetic anisotropy, such as surface, shape, etc. Therefore, the coercivity trend observed in the present case cannot account for only magnetic anisotropy but, together with other results, it points toward the increase in magnetic anisotropy with the small replacement of Fe^{2+} with Co^{2+} ions in B-sites.

Figure 5a displays the M–H loops at 300 K for $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles. For all the nanoparticles, the magnetization saturate is ~ 9000 Oe, without notable coercivity, H_C , and remanence (Figure 5a). The lack of notable H_C and remanence at 300 K (above the T_B) confirms the superparamagnetic-like nature of the nanoparticles. The saturation magnetization (M_S) at 300 K as a function of Co content ($x = 0-1$) is shown in Figure 5b and Table 2. The values of M_S remained almost constant with increasing Co content. These M_S values (~ 60 emu/g) are smaller than those of bulk CoFe_2O_4 and bulk Fe_3O_4 . The little variation in M_S with Co content could be due to the small difference in size and

crystallinity of the nanoparticles. The relatively high values of M_S for the $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles confirm the high crystalline quality. Owing to the enhanced magnetocrystalline anisotropy with the Co addition, the $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles are expected to show SAR enhancement. AC hyperthermia experiments via the calorimetric method were conducted on the $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles to demonstrate this.

Figure 4. (a) M–H curve of 7 nm series of $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles at 10 K. (b) Variation of coercivity (H_C) at 10 K as a function of Co content.

Figure 5. (a) M–H curve of 7 nm $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles at 300 K. (b) Variation of saturation magnetization (M_S) at 300 K as a function of Co content, x .

An investigation and comparison of the SAR values of the $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles was conducted for the purpose of examining the effect of Co content on the heating efficiency of the $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles. The study involved the measurement of temperature vs. time at different strengths of the external AC magnetic field using a nanoparticle concentration of 1 mg/mL in water. The heating rate was directly proportional to the increasing magnetic field, and it was found that an external AC magnetic field $H_{AC} \geq 600$ Oe is required to attain the temperature range of 40–44 °C, where tumor cells are deactivated or destroyed. The heating efficiency of the nanoparticles, SAR can be calculated from the initial slope of the T vs. time curves ($\Delta T/\Delta t$) [51]:

$$\text{SAR} = \frac{\Delta T}{\Delta t} \frac{C_P}{\varphi} \quad (1)$$

where C_P is the heat capacity of the dispersion medium (4.186 J/g K for water) and $\varphi = 1 \times 10^{-3}$ is the mass of $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles per unit mass of water.

It was established that the SAR values decrease drastically upon reducing the applied external AC magnetic field (Figure 6a). It is generally known that the agglomeration of the nanoparticles, which results in sedimentation, has a negative effect on the SAR value.

However, in the present study, the oleic acid and oleylamine functionalized hydrophobic nanoparticles were phase transferred to the aqueous phase using TMAH as a capping agent. The TMAH-coated particles remained well dispersed in water during the hyperthermia measurement. Therefore, the effect of particle sedimentation on the hyperthermia response was negligible. The variation of the SAR at external AC applied magnetic fields of 600 and 800 Oe as a function of Co content (Figure 6b). Pure magnetite $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0$) showed poor heating efficiency even at an external AC applied magnetic field of 800 Oe; however, a reasonable value of the SAR was observed with a small amount of Co content. Similar to the T_B and H_C at 10 K, the SAR value showed an increase with an increase in the Co content until $x = 0.75$, above which it showed a decreasing trend (Table 2). This indicates that the SAR value of nanoparticles depends primarily on the magnetic anisotropy of the particles. As discussed above, the magnetocrystalline anisotropy in $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles shows a peak at $x = 0.75$; therefore, the peak in the SAR value at $x = 0.75$ indicates an important role of the magnetic anisotropy in hyperthermia heating of the present nanoparticles. The relatively smaller values of the SAR for $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($0.75 \leq x \leq 1$) nanoparticles, as compared to 20 nm nanocubes [40], could be attributed to the shape and small size of the nanoparticles. The SAR values are dependent on the size and crystallinity of the nanoparticles and are relatively smaller when the size of the nanoparticles is below 10 nm [52]. Our study demonstrates that the SAR value of the $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles varies not just with the size (they are almost the same for all the particles) and M_s but also with magnetocrystalline anisotropy of the particles, on par with the previous reports [35,36]. These results prove that the SAR value of the sub-10 nm $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ nanoparticles can be improved by partial substitution of Fe^{+2} with Co^{+2} ions.

Figure 6. (a,b) Specific absorption rate (SAR) of 7 nm series of $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles in water, measured at alternating current (AC) fields of 800, 600 and 400 Oe and 310 kHz.

4. Conclusions

In summary, we have demonstrated that the heating efficiency (SAR) of the $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$) nanoparticles improves with an increase in Co content up to $x = 0.75$, following which it decreases with a further increase of the Co content. Magnetic and hyperthermia measurements on the 7 nm series of spherical $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ nanoparticles have shown that the T_B and SAR follow a similar trend with a maximum at $x = 0.75$. Our study has revealed that the SAR value for the nanoparticles not only depends on the size and saturation magnetization, which were constant for the series, but also primarily on the effective magnetic anisotropy of the particles. Our results are in corroboration with the theoretical findings on $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0-1$), which showed a maximum of magnetic anisotropy for x to be $\sim 0.6-0.7$. The outcome of this study showed that the spherical $\text{Fe}_{3-x}\text{Co}_x\text{O}_4$ ($x = 0.6-0.7$) nanoparticles have the potential of a promising material for magnetic hyperthermia therapy.

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N.P.K. and S.B.A.; writing—original draft preparation, R.D. and M.-H.P.; writing—review and editing, R.D., N.P.K., S.B.A., M.-H.P. and H.S.; supervision, R.D., M.-H.P. and H.S.; funding acquisition, R.D., M.-H.P. and H.S. All authors have read and agreed to the published version of the manuscript.

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