Current Pharma Research
ISSN: 2230-7842
CPR 1(4), 2011, 300-305.

Preparation and Characterization of Superparamagnetic Magnetite (Fe_3o_4) Nanoparticles.

***M. Vimal Kumar Varma and P. Amareshwar.**
University College of Technology, Department of Pharmaceuticals and Fine chemicals, Osmania University, Hyderabad- 500 007, Andhra Pradesh, India.

Abstract
Magnetite (Fe_3O_4) nanoparticles have been successfully synthesized by three methods viz chemical co-precipitation, oxidative hydrolysis and composite fluid methods. The phase structures, morphologies, chemical composition, and magnetic properties of Fe_3O_4 nanoparticles have been characterized by X-ray diffraction, scanning & transmission electron microscopy and vibrating sample magnetometer (VSM). The results indicate that that magnetite particles prepared by all the three methods showed crystalline nature and confirmed the presence of Fe_3O_4 (311 peak)as evident from XRD data, particles were spherical to elliptical in co-precipitation method and composite fluids method but were elongated crystalline in oxidative hydrolysis method from TEM and SEM images. All the particles showed excellent magnetic properties with saturation magnetization ranging from 39.5 to 41.5 emu/g which was evident from VSM data. This article gives the development of compatible lab scale methods for the synthesis of nano sized magnetite particles which are biocompatible and biodegradable and can be used as magnetic cores for magnetic carrier systems and help in targeting of pharmacologically active product in the body on application of external magnetic fields.

Key Words
Magnetite, Chemical Co-precipitation method, oxidative hydrolysis, Saturation magnetization, crystallinity, X-Ray diffraction studies.

Introduction
Targeted, yet minimally invasive drug or radiation delivery, an important goal of modern medical pharmacotherapy, is being actively pursued worldwide. The rationale behind target-specific delivery of a medication to a site is two-fold: it is desirable to minimize the amount of drug dosed to the body that does not make it to the site to avoid systemic side effects and to minimize the cost associated with its application, and it is desirable to increase the concentration of a drug at a target site to increase its effectiveness. In general, this goal can be accomplished by injecting, a relatively small amount of an encapsulated medication into the blood stream, followed by collection and concentration of this pharmacological carrier at the desired region in the body, and then followed by controlled release and localized, specific and rapid interaction of this medication at the target organ or disease site[1-3]. Magnetic targeting is one of the best approaches being actively pursued for targeted drug delivery[4], targeted radiation therapy[5], targeted hyperthermia treatment[6-7], and even targeted blood embolization[8].

***Corresponding Author:**
vimal_pharma@yahoo.co.in

The idea behind magnetic drug targeting is that magnetic drug carrier particles can be attracted to and retained at a specific site in the body using an external magnetic field source produced by a magnet. The purpose of this magnet is to impart an attractive force on the magnetic drug carrier particles that is large enough to overcome the hydrodynamic force associated with blood flow in the circulatory system, which is the only major force that the magnetic drug carrier particles are exposed to in the human body. However there are three limitations associated with the use of traditional magnetic drug targeting techniques. First, the retention of the magnetic drug carrier particles is quite low due to the inherently weak nature of the magnetic force[9]. Second, sites that are more than a few centimeters deep in the body are difficult to target. With the strength of the magnetic field generated from a permanent magnet decreasing sharply with distance, the hydrodynamic force increasingly overwhelms the magnetic force as the depth of the target site increases[10-12]. Third, even if the first two limitations can be overcome, the controlled release and localized, specific and rapid interaction of the medication itself, at the target organ or disease site, must be sufficiently fast or sufficiently specific that

it has a chance to treat the disease as soon as it is released. To address the first two limitations described above, high gradient magnetic separation principles are being exploited as an important and necessary modification to the traditional magnetic drug targeting approach[13-14]. The general idea behind a magnetic drug targeting system based on the high gradient magnetic separation concept is the use of a ferromagnetic materials combined with an external magnetic field. Currently, there are few magnetic materials like Zinc, manganese, cobalt and Iron oxides are used as magnetic micro and nanocarriers in biomedical and biotechnological applications. Fe oxides, and especially magnetite (Fe_3O_4) and maghemite, are mostly used in such applications, either as a background material for magnetic fluids or as magnetic particles, covered or not with a thin layer of polymer or other biocompatible materials[15]. Amorphous magnetic materials, both as micro and nanoparticles, could be successfully used as magnetic carriers because of their specific magnetic properties. Most of these materials are corrosion resistant, mechanically hard, but magnetically very soft[16-19]. Magnetite (Fe_3O_4) is a common magnetic iron oxide, and it has a cubic inverse spinel structure with oxygen forming a FCC closed packing and Fe cations occupying the interstitial tetrahedral sites and octahedral sites[20]. The electrons can hop between Fe^{2+} and Fe^{3+} ions in the octahedral sites at room temperature, rendering magnetite an important part of half-metallic materials. Magnetite nanoparticles have been widely studied because of their applications in ultrahigh density magnetic storage media, biological labeling, tracking, imaging, detection, and separations, and ferrofluid. Various chemistry-based processing routes have been developed to synthesize nanosized magnetite particles, including coprecipitation or precipitation[21], sol–gel method, emulsions technique[22], mechanochemical processing[23], hydrothermal preparation[18] and DC thermal arc-plasma method[17]. This paper focuses on the development of compatible lab scale methods for the synthesis of this nano sized magnetite particles that can be used as magnetic cores for magnetic carrier systems and help in targeting of pharmacologically active product in the body on application of external magnetic fields.

Experimental

Reagents

All reagents used were available commercially and were of analytical grade. Poly ethylene glycol 10,000 Sisco Lab Pvt Ltd, Poly ethylene sorbitan monolaurate (Tween 20) Loba-Chemie Pvt ltd, Mumbai, Ferric chloride ($FeCl_3$ $6H_2O$) SD Fine chemicals Ltd, Ferrous chloride ($FeCl_2$ $4H_2O$) HI-Media labs Pvt Ltd, Ferrous sulphate ($FeSO_4$) SD Fine chemicals Ltd, Sodium hydroxide (NaOH) Qualigens Fine chemicals, Oleic acid SD Fine chemicals Ltd, Hydrochloric acid (HCl) SD Fine chemicals Ltd, Potassium nitrate (KNO_3) Fischer scientific Ltd, Potassium hydroxide (KOH) Thomas bakers chemicals, Ammonium hydroxide (NH_4OH) Sisco Lab Pvt Ltd, Sodium di-hydrogen phosphate anhydrous SD fine-chemicals limited, and Ammonia solution Ranbaxy laboratories limited. Deionized water was used for the preparation of all aqueous solutions.

Preparation of magnetite particles/magnetic Ferro fluids

Magnetic Ferro fluids/Magnetite particles were prepared by employing three techniques.

1. By chemical co-precipitation method:
2. By oxidative hydrolysis
3. Composite magnetic fluids

Chemical co-precipitation method

Stoichiometric ratio of 1:2 ferrous sulfate hepta-hydrate ($FeSO_4$_$7H_2O$) and ferric chloride hexa-hydrate ($FeCl_3$_$6H_2O$) was dissolved in deionized water under vigorous stirring to prepare total concentration of 0.20-M ferrite solution as an iron source. Concentrated ammonia was then dissolved in an aqueous solution to form 3.5-M ammonium hydroxide (NH_4OH) as a base source. A 50-ml ferrite solution was mixed with appropriate amount of urea and the mixture was heated gently up to 80–100^oC in order to decompose the urea. Thus, the pH can be changed homogeneously all over the mixture. After that, during rigorous stirring, the mixture was titrated to have a pH of around 10–11 by adding drops of 3.5-M ammonium hydroxide at room temperature. It was observed that the solution became black due to the formation of Fe_3O_4 particles. The black mixture was then heated at 60–70^oC in a water bath for 30 min. Aggregates were then removed by centrifugation in a low speed centrifuge at 4000 rpm for 5 min. The purified water-based magnetic fluid containing Fe_3O_4 nano-

particles collected in the void volume had a concentration of about 10 mg Fe/ml.

Oxidative hydrolysis

Magnetite particles were synthesized by oxidative hydrolysis of a ferrous sulphate solution in an alkaline medium. A solution of 6.46 g KNO_3 and 44.9 g KOH in 240 ml distilled water was added drop-wise over 5 min to a solution of 80 g $FeSO_4$ _ $7H_2O$ in 560 ml water and heated to 90^oC. The solution was stirred continuously using a magnetic stirrer. This reaction typically yields approximately 23 g of magnetite. To limit the growth of the magnetite particles, 14.4 ml oleic acid (90%) was added 15 min after the addition of a KNO_3/KOH solution. The reaction vessel was immediately removed from the heat, and allowed to cool, reaching 40^oC in an hour under continuous stirring. Subsequently, the solution was acidified to pH 3 by the addition of dilute nitric acid. Addition of hexane to this solution causes magnetite to separate into the organic phase, indicating functionalization of the magnetite by the oleic acid. The magnetite powder was collected and dried.

Composite magnetic fluids

Magnetic fluid was synthesized as follows: a 35% (w/v) ferrous sulfate solution, 54% (w/v) ferric chloride solution and 36% (w/v) sodium hydroxide solution were prepared using distilled water. Then the ferric salt and ferrous salt were mixed, stirred and heated. When the temperature reached 55^oC, the alkaline solution was added. The mixture was stirred for 30 min, and then 5 g of polyethylene glycol-10000 (PEG-10,000) and 12ml of oleic acid was added. The temperature was raised to 80^oC and maintained for 30 min. The mixture was then neutralized while cooling, and the magnetic fluid was prepared which was collected and stored in a suitable container until further use. Factors like pH of solution and stirring speed (RPM) played an important role in governing the size of magnetite particles. Co-precipitation method and oxidative hydrolysis method yielded magnetite which was water insoluble and could be suitable for polymers which are organic in nature while the magnetite prepared using composite magnetic fluids was water soluble suitable for water soluble polymers. In both the cases drug can be independently varied i.e. both water soluble and water insoluble drugs can be used which in turn depends on the nature of the polymer.

The prepared magnetic material/ magnetic ferro fluids were characterized for its crystallographic nature and size determination and distribution by X-ray diffraction studies (XRD), magnetization properties were characterized by vibrating sample magnetometer (VSM) while surface morphology by transmission electron microscopy (TEM).

Results and Discussion

Characterization of magnetite nanoparticles

Fig 1 (a) shows the TEM image of magnetite particles prepared by Chemical co-precipitation method, it can be observed that the particles are well defined spherical to elliptical in shape with mean diameter of 24 $\pm$ 15 nm. Fig 1 (b) shows the TEM image of magnetite particles prepared by oxidative hydrolysis method. It can be observed that the particles were crystalline in nature with sharp edges. The physical nature of the prepared magnetite powder was greatly influenced by the reaction mixture and the pH maintained during the reaction.

Fig 1(c) shows the SEM image of the magnetite particles prepared as composite magnetic fluids. The sample was initially dried and SEM was performed. The particles were observed to be more irregular and non-uniform in nature. Fig. 2 shows the XRD patterns of the synthesized Fe_3O_4 particles by different methods. It is clear from the graph that only the phase of Fe_3O_4 is detectable. There is no other phase such as $Fe(OH)_3$ or Fe_2O_3, which are the usual co-products in a chemical co-precipitation and oxidative hydrolysis methods. The results shown in Fig. 2 reveal a high purity for the synthesized Fe_3O_4 magnetic particles. With the XRD pattern, the average core size of the particles can be evaluated from Scherrer equation.

$$\mathbf{L = 0.94\lambda/B\,(2\theta)\cos\theta}$$

Where, L is equivalent to the average core diameter of the particles, λ is the wavelength of the incident X-ray, B(2θ) denotes the full width in radian subtended by the half maximum intensity width of the powder peak, for instance (311), and θ corresponds to the angle of the (311) peak. For the (311) peak in the XRD pattern shown in Fig. 2 (a) for the magnetite obtained by chemical co-precipitation method, 2θ is observed as 35.64, and B (2θ) is 0.5360. With λ being 0.13678 nm, L is obtained as 26.56 nm via the above equation.

In case of magnetite obtained by oxidative hydrolysis and composite fluids from fig 2(b) and

2(c), 2θ is observed as 35.825 and 35.73 respectively, and B (2θ) was 0.6400 and 0.5892 respectively. With λ being 0.13 nm, L is obtained as 19.11 and 20.74 nm respectively. It can be observed that the FWHM values increases from one method to other which indicates there is increase in the crystallinity of the magnetite and the order of increase in crystallinity by three methods can be given by Chemical co-precipitation method < composite fluids method < oxidative hydrolysis method. Fig. 3 gives the magnetization loop of Magnetite particles at room temperature. The magnetic hysterestic curve exhibits superparamagnetic behavior. The main source of information about the magnetic properties of a ferromagnetic material as magnetite is the evaluation of the field dependence of the magnetization at a constant temperature, and, in particular, the characteristics of the hysteresis cycle / loop. This is done in Fig. 3 for magnetite prepared by all the three methods. It can be seen that all the three types of material exhibit similar overall magnetic behavior, characteristic of soft magnetic particles, with a narrow hysteresis cycle, and a small coercive field and remanent magnetization. The saturation magnetization of Fe_3O_4 particles at 8000 G were found to be 40.99, 41.45 and 35.99 emu/g for chemical co-precipitation, oxidative hydrolysis and composite fluids respectively which are in good agreement with magnetic data reported on magnetite.

Conclusion

Magnetite particles were prepared by three different methods viz chemical co-precipitation method, oxidative hydrolysis and composite fluids method. It can be observed that magnetite particles prepared by all the three methods showed crystalline nature and confirmed the presence of Fe_3o_4 (311 peak)as evident from XRD data, particles were spherical to elliptical in co-precipitation method and composite fluids method but were elongated crystalline in oxidative hydrolysis method from TEM and SEM images. All the particles showed excellent magnetic properties with saturation magnetization ranging from 39.5 to 41.5 emu/g as evident from VSM data. This paper gives the development of compatible lab scale methods for the synthesis of this nano sized magnetite particles which are biocompatible and biodegradable that can be used as magnetic cores for magnetic carrier systems and help in targeting of pharmacologically active product in the body on application of external magnetic fields.

Acknowledgment

This work was supported by University college of Technology, Osmania University, Hyderabad and Nalla Narsimha Reddy Educational Society's Group of Institutions.

References

1. Misael O, Avile S, Armin D. Ebner and James A. Ritter J. Magn. Magn. Mater. 2007, 310, 131–144.
2. Horia Chiriac, Anca-Eugenia Moga, Gheorghe Iacob, Ostin C. Mungiu J. Magn. Magn. Mater. 2005, 293, 28–32.
3. Jing Xu, Haibin Yang, Wuyou Fu, Kai Du, Yongming Sui, Jiuju Chen, Yi Zeng, Minghui Li, Guangtian Zou J. Magn. Magn. Mater. 2007, 309, 307–311.
4. Wanquan Jianga, Yanga H C , Yang S Y, Horngb H E, Hung J C, Chen Y C, Chin-Yi hong J. Magn. Magn. Mater. 2004, 283, 210–214.
5. Li F S, Wang L, Wang J B, Zhou Q G, Zhou X Z, Kunkel H P, Williams J. Magn. Magn. Mater. 2004, 268, 332–339.
6. Salim Md, Shukla V K, Bhardwaj V, Garg V K and Sharma P K Journal of global pharma technology. 2010, 2(3), 36-46.
7. Morais P C Journal of Physics: Conference Series 217 (2010) doi:10.1088/1742-6596/217/1/012091: International Conference on the Applications of the Mossbauer Effect (ICAME 2009).
8. Hafeli U O Int J Pharm. 2004, 277, 19–24.
9. Jurgons R, Seliger C, Hilpert A, Trahms L, Odenbach S, Alexiou C J. Phys: Condens. Matter. 2006, 18 S2893–S2902 doi:10.1088/0953-8984/18/38/S24.
10. Rahisuddin, Pramod K. Sharma, Mohd Salim, Garima Garg Int. J. Pharm. Sciences review and research. 2010, 5(3), 115-119.
11. Sonal A. Patil,. Suryawanshi H P, Sunil R. Bakliwal, Sunil P. Pawar International Journal of Pharma Research and Developmen.t 2010, 2(10), 25-29.
12. . Gomez-Lopera S A, Plaza R C and Delgado A V Journal of Colloid and Interface Science 2001, 240, 40–47.

13. Vidyavati S, Koppisetti, Sahiti. B Int. J. Drug Dev. & Res, 2011, 3(1), 260-266.
14. T.K. Indira, P.K. Lakshmi Magnetic Nanoparticles – A Review International Journal of Pharmaceutical Sciences and Nanotechnology 2010: 3(3): 1035-1042.
15. Zefeng Xia, Guobin Wang, Kaixiong Tao, Jianxing Li J. Magn. Magn. Mater. 2005, 293, 182–186.
16. Ramazan Asmatulu, Michael A. Zalich, Richard. O. Claus, Judy S. Riffle J. Magn. Magn. Mater. 2005, 292, 108–119.
17. Rasim A. Ali-zade Turk J Phys 2004, 28, 359-368.
18. Andreas S. Lubbe, Christian Bergemann, Jeffery Brock, David G. McClure; J. Magn. Magn. Mater.1999, 194, 149-155.
19. Daniel Horak, Eduard Petrovsky, Ales Kapicka, Theodor Frederichs; J. Magn. Magn. Mater. 2007, 311, 500–506.
20. Liu Z L, Ding Z H, Yao K L, Tao J, Du G H, Lu Q H, Wang X, Gong F L, Chen X J. Magn. Magn. Mater. 2003, 265, 98–105.
21. Nishio K, Ikeda M, Gokon N, Tsubouchi S, Narimatsu H, Mochizuki Y, Sakamoto S, Sandhu A, Ab M, Handa H J. Magn. Magn. Mater. 2007, 310, 2408–2410.
22. Muniyandy Saravanan, Kesavan Bhaskar, Gomathinayagam Maharajan, Kalathil Sadasivan Pillai Int. J. Pharm. 2004, 283, 71–82.
23. Sussan Ghassabian, Turaj Ehtezazi, Seyed Mohsen Forutan, Seyed Alireza, Mortazavi Int J Pharm, 1996, 130, 49-55.

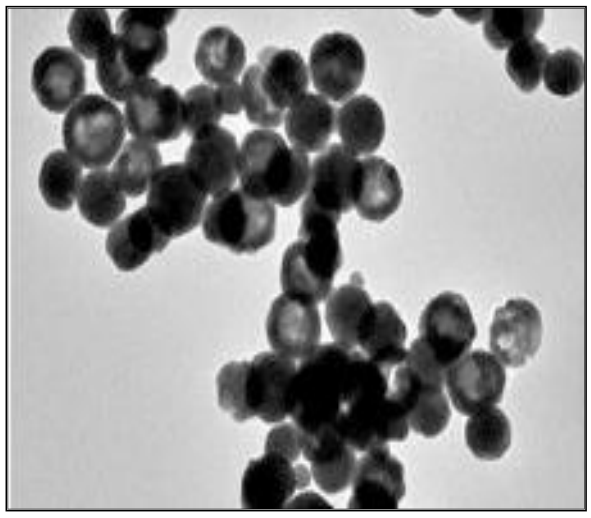

Fig 1 (a)

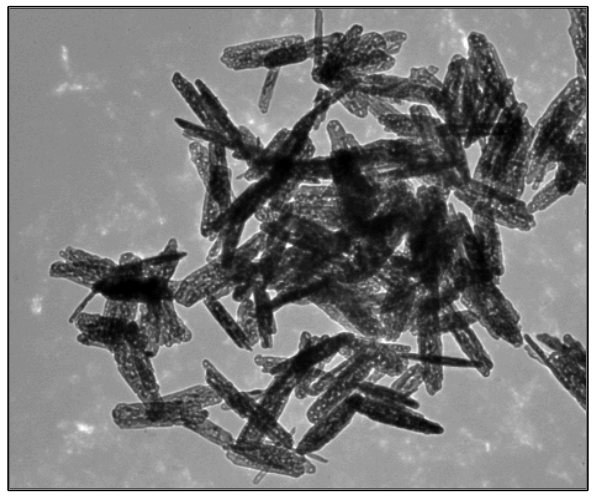

Fig 1 (b)

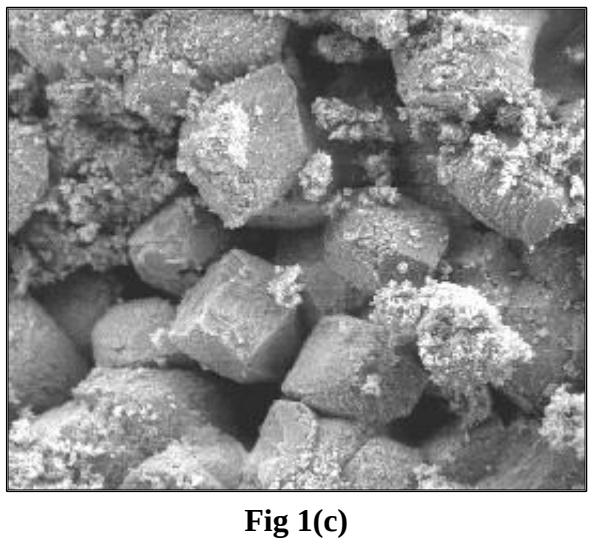

Fig 1(c)

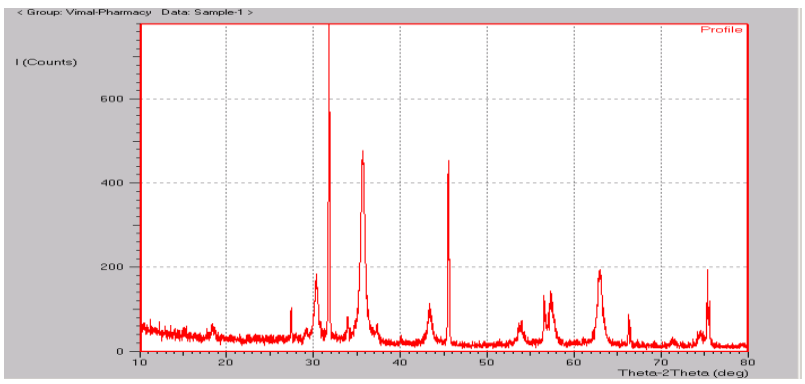

Fig 2(a)

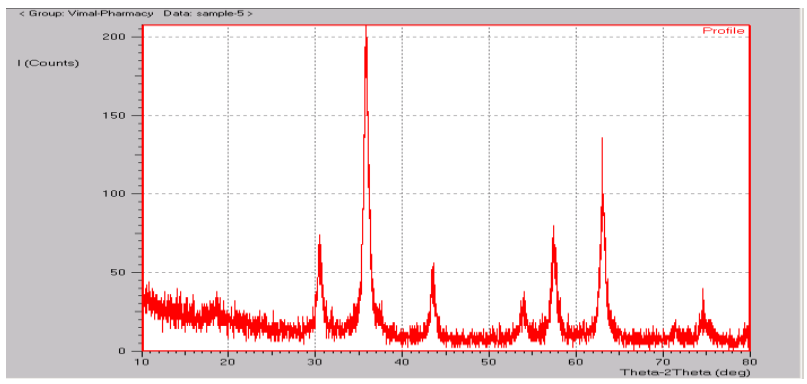

Fig 2(b)

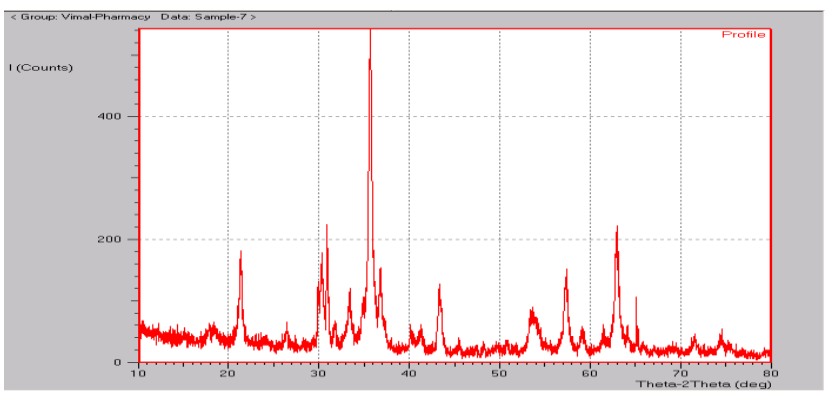

Fig 2(c)

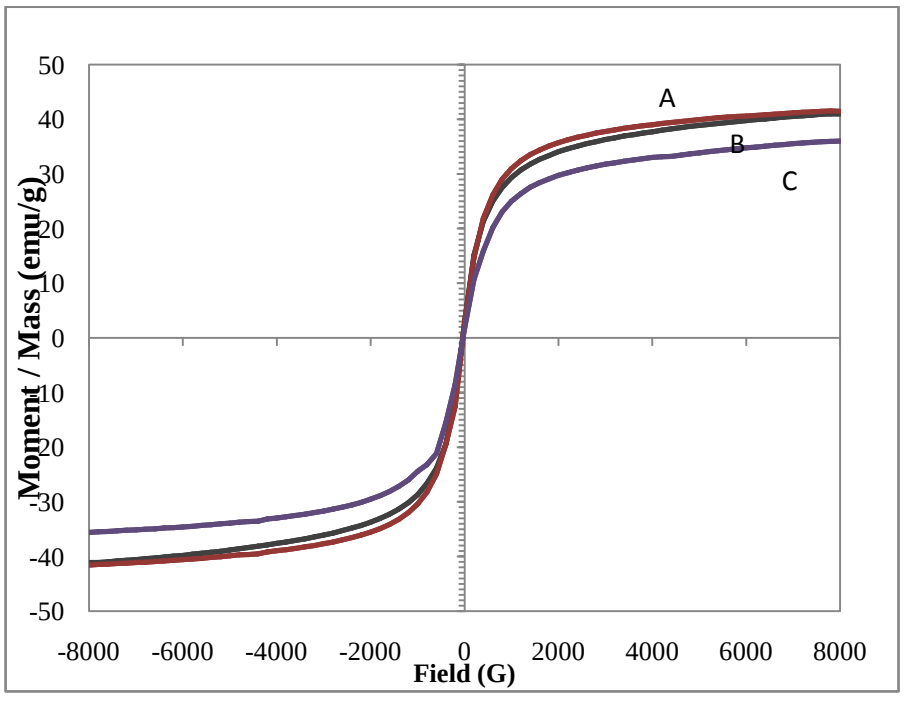

Fig 3: Magnetization curves for Oxidative Hydrolysis (A), Chemical Co-precipitation method (B) and Composite fluids (C).

******