International Journal of Pharmaceutics 365 (2009) 131–135

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical nanotechnology

Preparation, characterization and dielectric studies on carbonyl iron/cellulose acetate hydrogen phthalate core/shell nanoparticles for drug delivery applications

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ARTICLE INFO

Article history:
Received 25 April 2008
Received in revised form 6 August 2008
Accepted 7 August 2008
Available online 19 August 2008

Keywords:
Cellulose acetate hydrogen phthalate
Carbonyl iron
Core/shell
Dielectric constant
Drug delivery

ABSTRACT

A method to prepare composite colloidal nanoparticles, consisting of a magnetic core (carbonyl iron) and a biodegradable polymeric shell (cellulose acetate hydrogen phthalate) was described and also particle size was characterized by Optical Microscope and Scanning Electron Microscopy. Dielectric properties of Cellulose Acetate Hydrogen Phthalate (CAP) and carbonyl iron/CAP (core/shell) tablets were studied in the frequency range of 70 Hz–400 kHz at 300 K using LCR meter and compared the dielectric parameters of core/shell and ordinary phase of CAP tablets. From the dielectric results, the importance of core/shell nanoparticles in controlled drug delivery was discussed.

1. Introduction

Dielectric spectroscopy is an analytical technique which involves the application of an oscillating electric field to a sample and the measurement of the corresponding response over a range of frequencies, from which information on sample structure and behaviour may be extrapolated. This method has recently applied to a number of pharmaceutical systems (Sutananta et al., 1995; Craig, 1995; Benoit et al., 1994, 1996; Martin et al., 2003; McLoughlin et al., 2003).

Cellulose derivatives have been commonly used in controlled release drug delivery systems. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. In addition, materials have been developed that should lead to targeted delivery systems, in which a particular formulation can be directed to the specific cell, tissue, or site where the drug it contains is to be delivered (Vijayalakshmi Rao et al., 2000; Siepmann and Peppas, 2001; McCrystal et al., 2002; Hyuk Kim et al., 2003; Mario et al., 2004; Qing et al., 2007).

Because of their unique physical properties (regarding size and shape, magnetic characteristics, biocompatibility, etc.), magnetic colloids in the submicrometric and nanometric size ranges have found increasing and very promising applications in the biomedical field, particularly in drug delivery (Arias et al., 2006).

Magnetically controlled drug targeting is currently one of the most active areas of cancer research and one of the principal possibility of active drug targeting, that will allow the guidance of drug carriers to specific cells in a manner that differs from its normal distribution in the organism, selectively delivering anticancer drug molecules to the diseased site without a concurrent increase in its level in healthy tissues.

Carbonyl iron (Fe0) is a well-known material, a unique form of elemental iron (because of its small particle size), properly characterized in many aspects, that was chosen to serve as the magnetic nuclei and to set the size of the particles and it is low toxic. The polymeric shell could transport the drug and release it during its biodegradation (Arias et al., 2001, 2006). Arias et al., have reported the carbonyl iron core with different polymers like poly (ethyl-2-cyanoacrylate), poly (butyl cyanoacrylate), ethyl cellulose etc. for controlled drug delivery (Arias et al., 2001, 2006, 2007). In this work, we have chosen cellulose acetate hydrogen phthalate which is a free flow powder and easily biodegradable. The composition of CAP is phthalate content ~30–40%, acetyle content ~19–24%, hydroxyl content ~36–51% and its viscosity average molecular weight is $M_V = 70{,}000$. Among the cellulose based

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doi:10.1016/j.ijpharm.2008.08.006

polymers, only ethyl cellulose (Arias et al., 2007) has been used to prepare core/shell nanoparticles, and we report here for the first time, CAP is used to synthesize core/shell nanoparticles. Due to the presence of specific hydrogen bonding interaction, it has very wide applications in pharmaceutical industry (Rao et al., 1999).

We prepared the carbonyl iron core, CAP shell and carbonyl iron/CAP (core/shell) nanoparticles. It was characterized by Scanning Electron Microscopy and Optical Microscope. We prepared the CAP and carbonyl iron/CAP tablets with mixture of binders. We measured the dielectric parameters of these tablets.

2. Materials and methods

2.1. Materials

E. Merk variety of chemicals was used without further purification.

2.2. Methods

*Synthesis of carbonyl iron, CAP shell and carbonyl iron/CAP (*core/shell*) nanoparticles*: The method followed to obtain core/shell by Arias et al. (2007). It is based on the crystallization of a gel of amorphous ferrous hydroxide. The preparation of latter involved, mixing two solutions that were previously flushed with pure N_2 in order to eliminate as much dissolved oxygen as possible. The presence of oxygen in the medium promotes the formation of a large quantity of non-magnetic goethite [FeO·(OH)] as a secondary product. The first solution was prepared by mixing 10 ml of a 5 M KOH solution, 100 ml of a 2 M KNO_3 solution, and 864 ml of pure water. The second solution was prepared by mixing 0.1 ml of 1:1 96% H_2SO_4 in water with 27.8 g $FeSO_4 \cdot 7H_2O$ and 100 ml of water (1 M concentration of ferrous sulfate). Then 26 ml of this solution was added to the first solution.

Immediately upon mixing, a gel was formed. After being flushed with N_2, it was placed in an oil bath preheated to $90 \pm 1\,^{\circ}C$, and aged at this temperature for 4 h. After completion of this aging, magnetic particles were visible and their cleaning was achieved by magnetic separation: the solids were repeatedly separated from the liquid medium by using a permanent magnet, and redispersed in pure water. Non-magnetic dispersed material (elongated goethite particles) will be present during the first few repetitions. So the process is repeated for seven cycles. The particles were then dried at 60 °C in a vacuum oven and stored until use.

To obtain the Cellulose Acetate Hydrogen Phthalate (CAP) latex, 4.68 g of CAP was dissolved in 26.57 g of dimethyl sulphoxide. After 24 h at room temperature, 0.31 g of cetyl trimethyl ammonium bromide was added to the polymeric phase, and it acted as a stabilizer of the emulsion prepared by adding this organic solution to 94 g of a 10^{-3}N HNO_3 aqueous solution, containing 0.125% (w/v) sodium dodecyl sulphate and 0.375% (w/v) polyethylene glycol 6000. Before mixing, both phases were heated at $67.0 \pm 0.5\,^{\circ}C$, and the incorporation of the aqueous phase to the polymeric one was carried out under mechanical stirring at 4000 rpm, during 5 min. Finally, the organic solvent was evaporated at room temperature and under mechanical stirring at 2000 rpm, during 24 h, in order to eliminate the toxicity of the systems and to increase their solid content. A whitish suspension was obtained, which was then subjected to a cleaning procedure that included repeated cycles of centrifugation and redispersion in Milli-Q water.

Finally, the procedure followed to obtain the core/shell nanoparticles was very similar to the one described for the latex spheres, except that the aqueous phase was a 0.266% (w/v) carbonyl iron suspension in 10^{-3}N HNO_3 solution. This initial polymer/magnetic nuclei weight ratio has been shown to produce an adequate polymer shell on the magnetic nuclei. Cleaning was achieved by repeated magnetic separation and redispersion in Milli-Q water leads to the formation of core shell nanoparticles. It was characterized by Scanning Electron Microscopy (Leica Stereoscan 440) and Optical Microscope (Olympus Bx61-33MU).

Using the wet granulation methods, we prepared the two tablets, (i) mixture of 60% CAP with binders (starch and magnesium and talc) (ii) mixture of 60% carbonyl iron/CAP core Shell nanoparticles with binders. Dielectric properties of these tablets were studied in the frequency range of 70 Hz–400 kHz at 300 K using Hioki 3532-50 LCR meter.

3. Results

3.1. Particle size

Figs. 1–2 show the Optical Microscope pictures of core, and core/shell particles. Fig. 3 shows the Scanning Electron Microscopy images of CAP Shell particles.

3.2. Principles of dielectric analysis

Dielectric analysis involves the application of a sinusoidal electric field to a sample and the measurement of the corresponding response over a range of frequencies. In the simplest case, one can consider the sample to be composed of a set of dipoles which will reorientate with the field, thereby generating a polarization

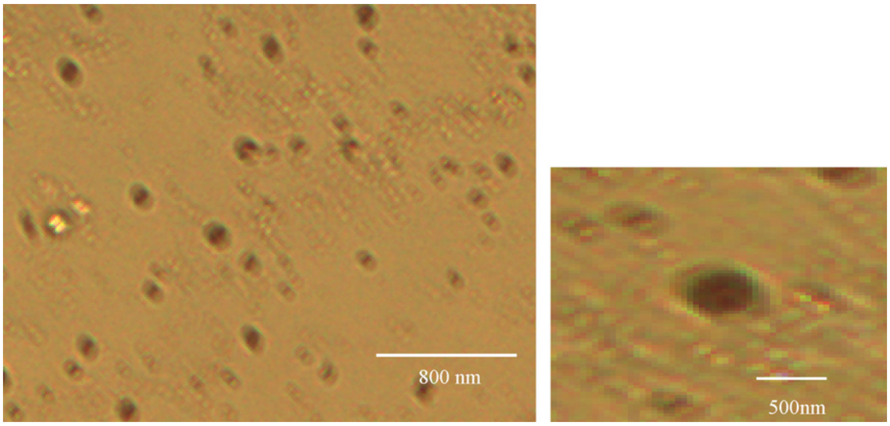

Fig. 1. Optical microscope pictures of carbonyl Iron average size of particles: 647 nm.

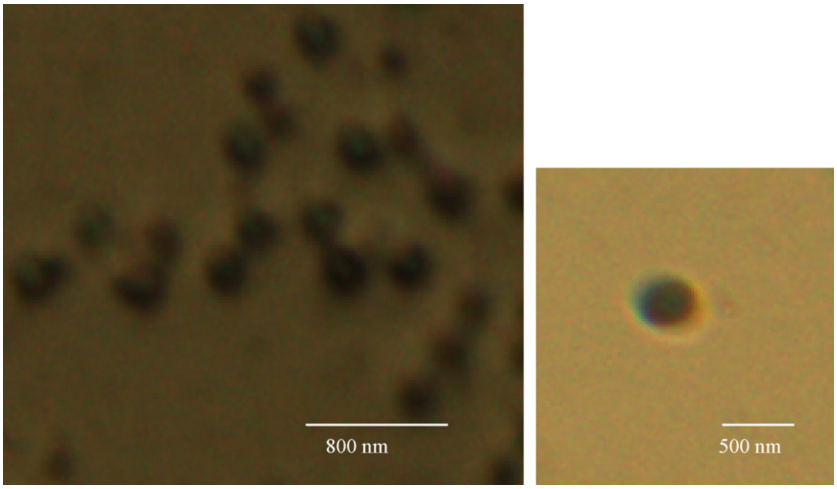

Fig. 2. Optical microscope pictures of core/shell nanoparticles. Average particle size: 700 nm.

current. The efficiency of this dipolar response will be frequency dependent; at any frequency, some energy will be stored by the system in the form of the reorientation process while some energy will be lost as heat (Sutananta et al., 1995; Craig et al., 1997).

The nature and significance of the dielectric response can be best visualised by considering the polarization (P) generated in a sample subjected to a unidirectional field of magnitude E, given by

$$P = (\varepsilon_r - 1)\varepsilon_0 E \tag{1}$$

where ε_r, is the relative permittivity (dielectric constant) and ε_0 is the permittivity of free space, which has a constant value. In an alternating field, the polarization will be frequency dependent and may be given by

$$P^*(\omega) = \varepsilon_0 i \chi^*(\omega) E^*(\omega) \tag{2}$$

where $P^*(\omega)$ and $E^*(\omega)$ are the polarization and field at frequency ω, while χ is the susceptibility of the sample, which is an intrinsic property of the material and hence contains information on the material structure and behaviour. As it is necessary to consider both the magnitude and phase behaviour of the response, it is convenient to express the susceptibility as a complex variable (denoted by *), i.e.

$$\chi^*(\omega) = \chi'(\omega) - i\chi''(\omega) \tag{3}$$

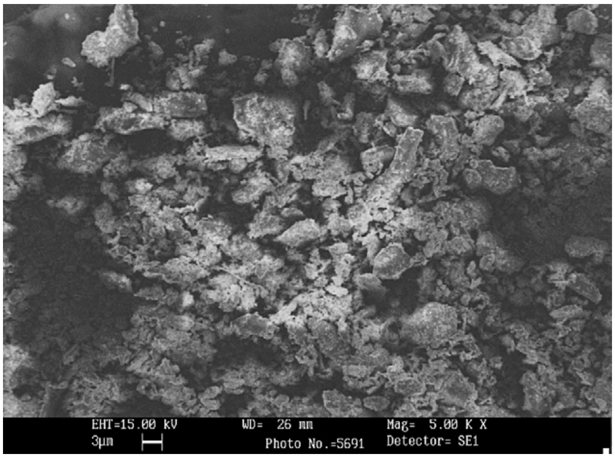

Fig. 3. SEM image of shell (polymer).

where $\chi'(\omega)$ and $\chi''(\omega)$ are the real and imaginary components of the susceptibility and are a reflection of the energy stored and lost within the system, respectively. The susceptibility is mathematically related to the permittivity, which is often used in the dielectric literature, given by

$$\varepsilon^*(\omega) = \varepsilon'(\omega) - i\varepsilon''(\omega) \tag{4}$$

with the relationship between the two parameters given by

$$\varepsilon^*(\omega) = \varepsilon_0 \left\{ 1 + \sum \chi'(\omega) \right\} - i \sum \chi''(\omega) \tag{5}$$

The real and imaginary parts may not be measured directly. In practice, the dielectric response of a sample is measured in a capacitance cell, conventionally consisting of two electrodes of parallel plate geometry of plate area A and spacing d. The oscillating field is applied to the sample over a wide range of frequency and the capacitance (C) and dielectric loss G/ω, where G is the conductance, are monitored. The real and imaginary parts of susceptibility are related to these observed parameters by Eqs. (6) and (7):

$$C(\omega) = \frac{A\varepsilon_0}{d}[\chi'(\omega) + \varepsilon(\infty)] = \frac{\varepsilon_0 \varepsilon'_r A}{d} \tag{6}$$

$$\frac{G(\omega)}{\omega} = \frac{A\varepsilon_0}{d}[\chi''(\omega)] = \frac{\varepsilon_0 \varepsilon''_r A}{d} \tag{7}$$

where ε_0 is the permittivity of free space ($8.854 \times 10^{-12}\,\mathrm{F\,m^{-1}}$); ε'_r and ε''_r are the real and imaginary parts of the relative permittivity of the sample, respectively. The relative permittivity is defined as the permittivity of the sample divided by that of free space (ε_0). Recently, dielectric analysis shows considerable promising results in the absorption of drugs onto polymeric pharmaceutical carriers, both in ionized and in non-ionized (Benoit et al., 1996; Martin et al., 2003).

Dielectric parameters such as capacitance (C), conductance (G), dielectric constant (ε'_r), and dielectric loss (ε''_r) at various frequencies are studied for CAP and core/shell nanoparticles composition tablets. The results are shown in Figs. 4–7.

4. Discussion

Sizes of carbonyl iron, polymer shell and the shape of core/shell nanoparticles were measured using Optical Microscope. The average size of carbonyl iron is 647 nm and core/shell nanoparticles is 700 nm. The surface morphology of polymer shell was done by SEM and the average size is 2–3 μm. The results support the

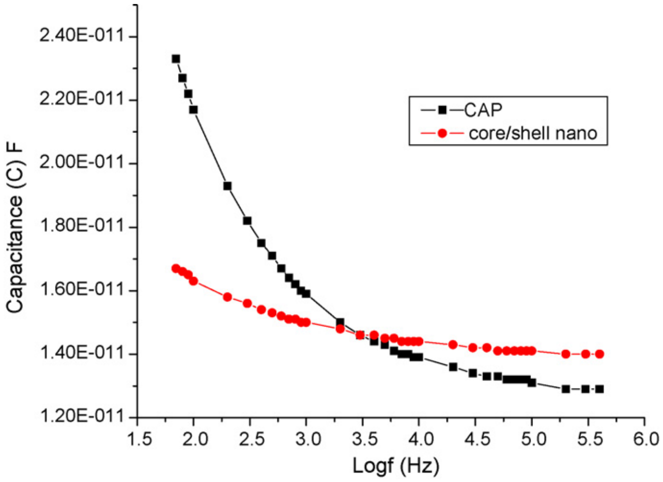

Fig. 4. Log frequency *vs* capacitance.

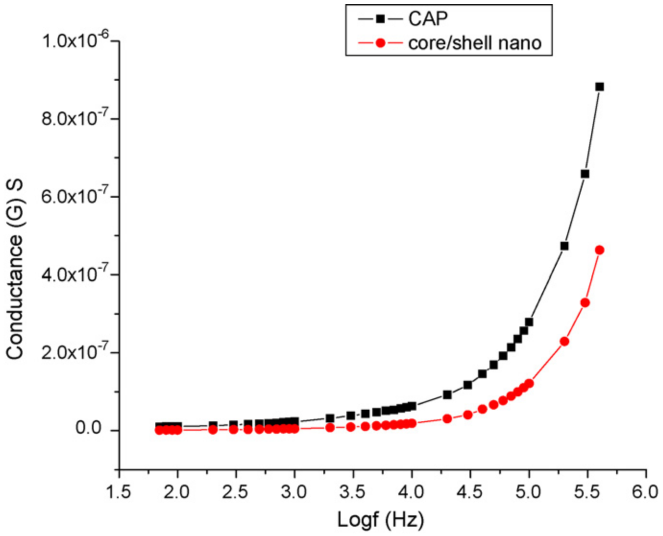

Fig. 5. Log frequency *vs* conductance.

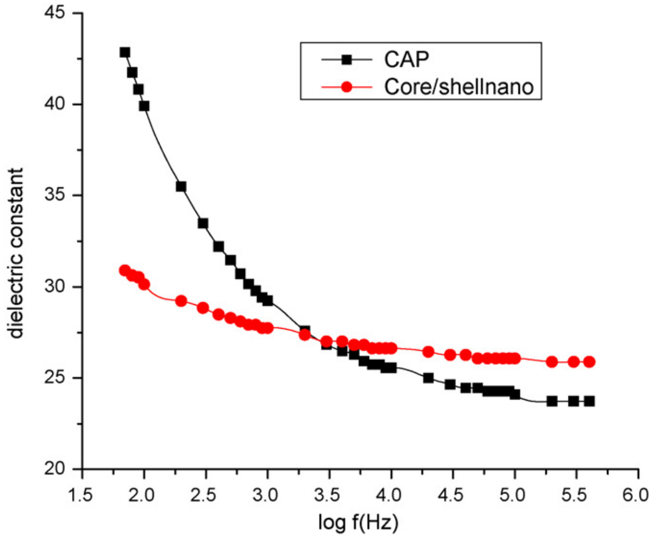

Fig. 6. Log frequency *vs* dielectric constant.

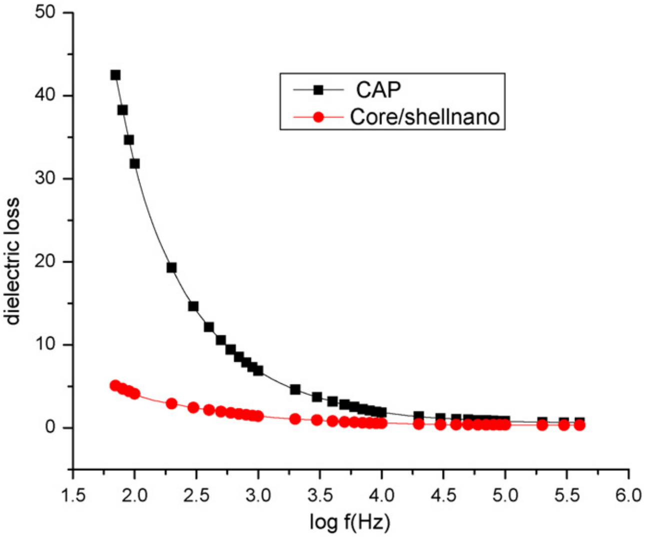

Fig. 7. Log frequency *vs* dielectric loss.

data obtained from Optical Microscope was matched with Arias et al. (2007). They studied carbonyl iron/ethyl cellulose core/shell nanoparticles.

The variation of dielectric parameters with temperature and frequency are different for polar and non-polar polymers. For polar polymers are highly dependent on temperature and frequencies, but for non-polar polymers are independent on temperature and frequencies. From our results, Figs. 4–7 show that the variation in the capacitance, conductance, dielectric constant and dielectric loss for our samples with respect to the various frequencies in the range of 70 Hz–400 kHz at 300 K.

From Fig. 4, it was observed that the capacitance decreases with increase in the frequency, hence the dielectric constant $(\varepsilon' \alpha C(\omega))$ also decreases with increase in the frequency as shown in Fig. 6. But in the case of conductance (Fig. 5) which increases with increase in the frequency, even though dielectric loss $(\varepsilon'' \alpha (G(\omega))/(\omega))$ is decreasing with increasing in the frequency (Fig. 7). From our results, all compositions are highly frequency dependent. This may be attributed to the tendency of the induced dipoles in the polymer to orient themselves in the direction of applied field (Vijayalakshmi Rao et al., 2000).

Our results show that dielectric constant and dielectric loss of CAP decreasing while increasing the frequency. But in the case of nanocomposition the dielectric constant and dielectric loss are almost constant even if we change the frequency. To obtain controlled release, the polymer material interaction among itself should be more, thereby reducing the interaction of surrounding matter. So, all pharmaceutical industries are using polymers as drug delivery system. We correlate in this report, the dielectric studies with controlled drug release is more for nanocomposite (core-shell) than polymers.

5. Conclusions

In this work, we have synthesized carbonyl iron/CAP core shell nanoparticles for the first time and their dielectric constant and dielectric loss were analyzed in over range of frequencies. We correlated the dielectric measurements with controlled drug delivery. The results of CAP core/shell nanoparticles showed sustained drug delivery compared to pure CAP tablets. It is therefore hoped that with further study, dielectric analysis may become a useful tool for the study of controlled drug delivery system.

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