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Sustained drug release and electrochemical performance of ethyl cellulose-magnesium hydrogen phosphate composite

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ABSTRACT

In this, a sol-gel method was applied to prepare ethyl cellulose-magnesium hydrogen phosphate (EC-$MgHPO_4$) composite that can have potential applications in the sensory, pharmaceutical, and biomedical sectors. The formed composite was thoroughly characterized by making use of the instrumental analysis such as UV–Vis, FT-IR, HRTEM, EDAX, SEM and XRD. For the composite, the other parameters determined includes the water uptake, porosity, thickness, bulk and tapped densities, angle of repose, Carr's index and Hausner ratio. From the results, the material found to exhibit good flowing properties with a Carr's index of 11.11%, Hausner ratio of 1.125, and angle of response of 33°. The EDAX spectrum and HRTEM analysis confirmed for the composite formation and the particles size is investigated to be around 52 nm. The surface porosity due to the EC matrices was confirmed by the SEM analysis, which further used for the loading of drug, Proguanil. In addition, the material's conductivity was studied by taking uni-univalent electrolyte solution (KCl and NaCl) indicated that the conductivity follows the order of KCl > NaCl, while the activation energy obtained from Arrhenius method resembled that the conductivity is strongly influenced by the electrolyte type used. We found from the analysis that, with a decrease in the size of hydrated radii of ions, the conductivity of EC-$MgHPO_4$ material also observed to be decreased in the order $K^+ > Na^+$ and the material proved to be mechanically stable and can be operated over a range of pHs, temperatures, and electrolyte solutions. Further, the drug loading and efficiency studies indicated that the material can trap up to 80% of Proguanil (antimalarial drug) applied for its loading. The Proguanil drug release profiles confirmed for the controlled and sustained release from the EC-$MgHPO_4$ matrix, as the material can release up to 87% of its total loaded drug over a 90 min period. Finally, the cell viability and proliferation studies tested against two different cell cultures of BRL-3A rat liver and H9c2 cardiomyoblasts indicated the non-toxic nature and safer applicability of the EC-$MgHPO_4$ (25–500 μg/mL, 24 h). Overall, the results of the study confirm for the safer applicability of the composite towards biosensor, drug delivery, scaffolding, and bioanalytical (quality control) applications.

1. Introduction

In the present scientific research, the organic-inorganic hybrid materials have gained much attention of researchers due to their outstanding mechanical properties combined with some other integrated characteristics such as thermally stable inorganic backbones, specific chemical reactivity and flexibility inorganic functional groups, in addition to non-toxic nature [1–5]. Thus formed hybrid material's inclined properties are highly dependent on their chemical composition, dynamic structure, porosity and other surface characteristics. The water dispersibility, solubility and mechanical toughness are some of the potential advantages offered by the hybrid composites. Also, in order to manufacture these composites, the sol-gel mediated formation of hybrid matrices was considered as the active means because of the creation of complex structures with high stabilities, minimum swelling properties, controlled cross-linking, and effective bond formation between the organic and inorganic segments [6–8].

One of the derivatives of cellulose, ethyl cellulose (EC) exhibits the properties of extensive linearity, chain stiffness, good solubility in organic solvents, good biocompatibility, high mechanical intensity, and stability which can be explored for the formation of hybrid composites in combination with various other materials [9]. It is considered to be one of the exclusive derivatives of cellulose obtained from inexhaustible natural polymers and is formed by the

Abbreviations: EC, ethyl cellulose; $MgHPO_4$, magnesium hydrogen phosphate; CBPC, chemically bonded phosphate ceramics; XRD, x-ray diffraction; EDAX, electron diffraction analysis by x-rays; FT-IR, fourier transform-infrared; HRTEM, high resolution transmission electron microscopy; SEM, scanning electron microscopy.

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conversion of the hydroxyl groups on the repeated glucose units into ethyl ether groups. The different applications of EC are in paper and textile coatings, gel lacquers, food additives as an emulsifier and on large extent, it is employed as a dissolution rate controlling polymer in sustained release dosage forms [10–11]. In addition, the physicochemical properties like compressibility, passive, and hydrophobic behavior especially attracted for its use in the preparation of lipophilic pharmaceutical dosage forms by taking advantage of its nontoxic, stable, ease of processing and low cost nature combined in a biodegradable form [12].

In recent years, the interesting properties of phosphate materials such as high thermal expansion coefficient, low glass transition temperature and low softening temperature have attracted attention of researchers [13]. Since, these materials are considered to be potentially eligible for making solid state electrolytes, machinable glass ceramics, amorphous semiconductors, laser glasses, optoelectronic and nuclear waste storage materials [14–16]. Among many other phosphates, the spectroscopic appearance of the vibration modes in the magnesium phosphate ($MgHPO_4$) compound is very complex at least due to the coupling effects and also due to the presence of Mg^{2+}, $H_2PO_4^-$ and H_2O species [17]. The magnesium phosphate cement, also called magnesium phosphate ceramics, falls into the category of chemically bonded phosphate ceramics (CBPC) and is highly crystalline in nature and is regarded as the room temperature-setting ceramics analyzed for the use of structural materials [18].

The analytical chemistry, process industry, food analysis and water-quality control are the various fields where the electrolyte conductivity measurements are highly applicable [19]. In addition, the medical fields like pharmacology, blood and urea analysis, tissue-perfusion measurements, chemical and biological sensing for the detection of a wide range of biochemical species such as amino acids, proteins, peptides, DNA, explosives and chemical warfare agents also takes the tools of conductivity measurements [20]. Further in pharmaceutical industry, it is highly important to report the powder flow properties of the crystalline/amorphous materials and for that, the physical parameters in general are measured by taking the thickness, water uptake, porosity, bulk density, tapped density, angle of response, Carr's index, and Hausner ratio. The bulk density of a powdered composite is denoted by the weight in a given volume (including interparticulate void volume), while the tapped density measures the density after mechanically tapping the container having the powder sample. The Carr's index is an indicative of powder bridge strength and stability, while the Hausner ratio represents interparticle friction.

With that, the objective of the present study was to prepare an inorganic-organic hybrid composite material which has the broader range of applications in the pharmaceutical and biomedical sector by taking advantage of its controllable properties of conductivity, biodegradability and surface adsorption. For that, we prepared a stable EC-$MgHPO_4$ composite using sol-gel approach involving EC as binder and $MgHPO_4$ of semiconductor material in a 1:3 wt/wt. ratio. We hypothesized that the formed hybrid composite of EC-$MgHPO_4$ be suitable for the integrated applications by taking advantage of its biodegradable and adsorption properties provided by EC (suitable for the controlled drug delivery applications), and electrochemical conductivity due to $MgHPO_4$ (offers biosensing capacity). The other applications of the formed composite can be in the filtration tasks in the beverage and textile industry, medicine, chemical industry, and waste-water treatment. All the above mentioned applications are ascribed to their high thermal and chemical resistances, mechanical strength, simplicity and low operation costs. In the study, the formed EC-$MgHPO_4$ composite was thoroughly characterized by using the instrumental analysis such as UV–Vis, FT-IR, HRTEM, SEM, EDAX, and powdered XRD measurements. Further, the composite was loaded with Proguanil, an *anti*-malarial drug to see its controlled biodegradable properties by means of investigating the release of the drug from the surface of EC due to the variations in pH, and temperature. Also, the conductivity behavior was investigated by measuring the electrochemical behavior under the influence of different solution mediums. Finally, the composite was tested for its toxicity following the treatment to two different cell cultures of BRL-3A rat liver cells and H9c2 cardiomyoblsts over a range of concentrations of 25–500 μg/mL for a 24 h period.

2. Experimental

2.1. Synthesis of EC-$MgHPO_4$ composite

The synthesis method for the preparation of EC-$MgHPO_4$ was similar to as followed by Arfin and Kumar [21]. Briefly, 0.2 M dipotassium hydrogen orthophosphate (98%, S.D. Fine-Chem Limited) was mixed with 0.2 M magnesium(II) chloride (99%, S.D. Fine-Chem Limited) to yield light white precipitate. To this mixture, dilute hydrochloric acid (35.4%, S.D. Fine-Chem Limited) was added so as to maintain the pH at 1.0 by stirring constantly for some time whereas the precipitate was kept at room temperature (24 h) for the observation. For the removal of free electrolytes, the precipitate was well washed with deionized water and was dried at 50 °C. By using a mortar and pestle, the dried precipitate was churned into powder and then sieved by using 85 μm sieve. The expected chemical equation is as given below:

$$MgCl_2 + K_2HPO_4 \rightarrow MgHPO_4 + 2KCl$$

To this, pure ethyl cellulose, EC (99%, S.D. Fine-Chem Limited) was employed as binder, grounded and sieved through 85 μm mesh. Different combinations of the ratio of precipitate and binder were analyzed so as to obtain the final composite material consisting of efficient mechanical strength and electrical conductivity. In that view, we found that the material prepared by embedding 25% EC was considered to be highly applicable for the experimentation. However, the material with high EC content was found to be stable but the electrical conductivity is becoming a major issue, while the composite of lesser amount of EC suffers from the issues related to mechanical instability. For the preparation of composite with 25% EC, we first placed 63 mg of EC and 187 mg of $MgHPO_4$ in an oven at 80 °C for about 30 min, and further increased the temperature to around 90 °C for 15 mins so as to equilibrate the reactants mixture. After cooling of the contents to room temperature, the tablets are formed by compressing the composite mixture using a Tablet compression (Mini press 1 station, Rimek). The tablets formed from the powder composite are shown in Fig. 1.

2.2. Measurement of material conductivity

The construction of concentration cells were organized to measure the material conductivity for evaluating the activation energy. For the

Fig. 1. Formation of tablets from the powdered composite of EC-$MgHPO_4$.