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Application of halloysite clay nanotubes as a pharmaceutical excipient

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ABSTRACT

Halloysite nanotubes, a biocompatible nanomaterial of 50–60 nm diameter and ca. 15 nm lumen, can be used for loading, storage and sustained release of drugs either in its pristine form or with additional polymer complexation for extended release time. This study reports the development composite tablets based on 50 wt.% of the drug loaded halloysite mixed with 45 wt.% of microcrystalline cellulose. Powder flow and compressibility properties of halloysite (angle of repose, Carr's index, Hausner ratio, Brittle Fracture Index, tensile strength) indicate that halloysite is an excellent tablet excipient. Halloysite tubes can also be filled with nifedipine with ca. 6 wt.% loading efficiency and sustained release from the nanotubes. Tablets prepared with drug loaded halloysite allowed for almost zero order nifedipine release for up to 20 h. Nifedipine trapped in the nanotubes also protect the drug against light and significantly increased the photostability of the drug. All of these demonstrate that halloysite has the potential to be an excellent pharmaceutical excipient that is also an inexpensive, natural and abundantly available material.

1. Introduction

Halloysite clay is a naturally formed tubular material with a chemical formula of $Al_2Si_2O_5(OH)_4$. These nanotubes have an outer diameter of 50 ± 10 nm, inner lumen of 15 ± 5 nm and length of 800 ± 300 nm (Fig. 1). The nanotube walls contain 10–15 closely packed aluminosilicate sheets with spacing of 0.72 nm between each layer. The surface of halloysite tubes is comprised of silica and its inner lumen is composed of alumina. Therefore, a strong negative zeta-potential of −35 mV on the tube's surface and a positive +25 mV within the inner lumen in aqueous dispersions at pH 4–8 are evidenced. Halloysite tubes are inert and stable in wide range of pH (3–10) (Lvov et al., 2016a,b). Halloysite was determined to be biocompatible through *in-vitro* studies of tissues and biological cells. Halloysite is safe if added to cell cultures, microworms or infusoria at a concentration of up to 0.5 mg/mL (Lvov et al., 2016a,b; Vergaro et al., 2010; Fakhrullina et al., 2015).

Since these nanotubes are readily available at a low cost and are biocompatible, they were successfully utilized in the past for the encapsulation and sustained release of a wide variety of drugs. The usual loading efficiency of the drugs within the lumen is 10–15 wt.% which corresponds to its 15 nm inner lumen volume. Halloysite can be used in its native form or functionalized to increase the drug loading efficiency. Halloysite was earlier used for the loading and sustained release of tetracycline, kellin and nicotinamide adenine dinucleotide (Fakhrullina et al., 2015). Furosemide, nifedipine, dexamethsone (Price et al., 2001), 5-amino salicylic acid (Veerabadran et al., 2007) and antiseptics (Aguzzi et al., 2013) were loaded into pristine halloysite, resulting in colloidal formulations.

The surface/lumen of halloysite was modified by 3-aminopropyltriethoxysilane, to load ibuprofen (Wei et al., 2014), aspirin (Tan et al., 2013), diclofenac sodium *via* hydrogen and ionic bonding (Lun et al., 2014) and triazolium salts to load curcumin also through its ionized/deionized states at various pH values (Hemmatpour et al., 2015). The inner lumen was etched using acid/base to increase loading of the antibacterial drug ofloxacin (Riela et al., 2014; Wang et al., 2014). By coating the nanotubes with dextrin/glycogen, the release of antiseptic agent Brilliant green was significantly decelerated. The loaded drugs were released *in vitro* at a sustained rate for a duration of 5–12 h (Wang et al., 2014). An additional polymeric encapsulation of the loaded tubes allowed for extended release for up to 50–100 h (Tully et al., 2016; Dzamukova et al., 2015).

Despite a wide range of halloysite drug composites being studied, none has been developed into any pharmaceutical

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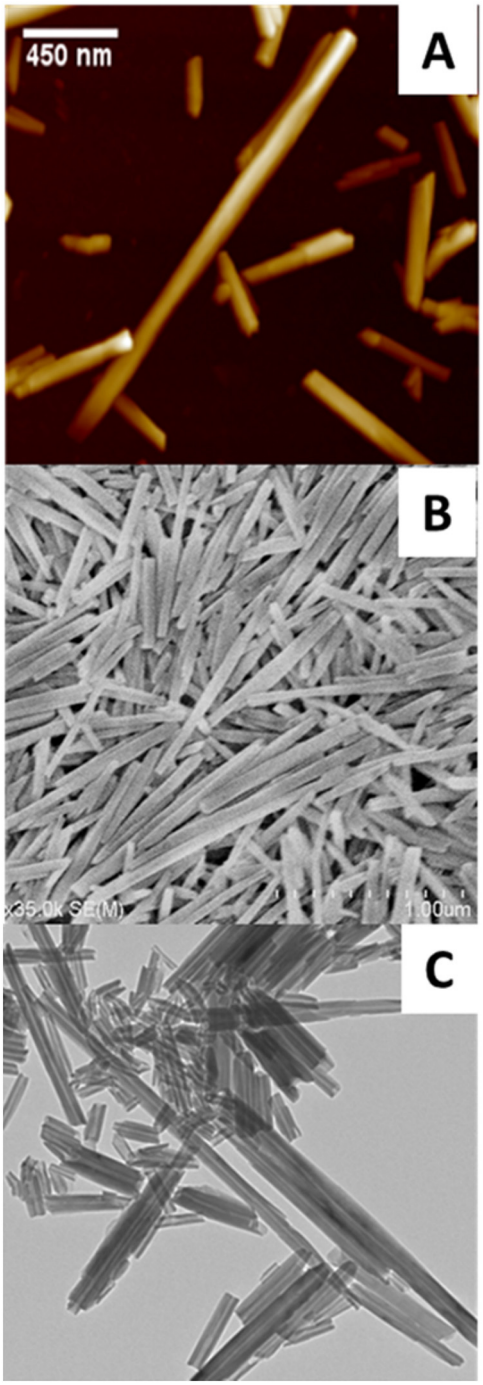

Fig. 1. Microscope images of halloysite nanotubes: (A) AFM, (B) SEM, (C) TEM.

formulation. Halloysite tubule clay cannot be used for injectable drug delivery because it is not biodegradable in blood and might cause thrombosis. Therefore, it has to be incorporated in an oral formulation, whereby systemic absorption of the halloysite is prevented. Animal studies conducted on chickens and piglets, indicated that halloysite can be safely delivered orally. Halloysite was used to treat these animals to remove mycotoxins such as zearalenone and deoxyvalenol sometimes occurring in grain feed given to these animals (Zhang et al., 2014). Kaolinite is a commonly used excipient in pharmaceutical preparations (Carretero and Pozo, 2009) and halloysite nanotubes are rolled sheets of kaolinite and can possibly be used as an excipient for the compression of tablets. An oral drug delivery system such as tablets or microcapsules with these clay nanotubes can be produced by blending halloysite commonly used tablet excipients and polymers.

This study introduce halloysite clay nanotubes as a tablet excipient with excellent compression properties and as a controlled-release drug delivery agent. Flow and compressibility properties indicated that halloysite by itself has good powder flow which changes to excellent when mixed with colloidal silica. Halloysite can also be loaded with drug nifedipine at 6 wt.% efficiency and then be incorporated into tablets by blending with microcrystalline cellulose (filler), colloidal silicon dioxide (gliding agent), magnesium stearate (lubricant) and croscarmellose sodium (disintegration agent). Nifedipine, an anti-hypertensive drug available in extended release dosage form, was used as a model drug to compare drug release from halloysite to commercially available formulations. The release of nifedipine from these tablets can sustained for up to 20 h through almost zero order release. In addition, when loaded into halloysite, light sensitive nifedipine can be protected from photo degradation.

2. Materials and methods

Halloysite clay was provided by Applied Minerals Inc, USA. Nifedipine was purchased from Sigma Aldrich. Excipients microcrystalline cellulose, magnesium stearate, croscarmellose, colloidal silica (aerosol 200 with diameter 5–20 nm) were supplied by Sigma Aldrich. A Carver auto bench top press (Wabash, IN) was used for preparing tablets. Varian VK 200 tablet hardness test unit (Varian, Paolo Alto, CA) was used to measure compressibility properties such as tensile strength, porosity and brittle fracture index. Thermogravimetric analysis was performed on a Thermal Advantage Q50. UV–vis analysis was performed using an Agilent spectrophotometer.

Scanning electron microscopy (SEM) images were obtained using Hitachi S-4800 field emission scanning electron microscope at 3.0 kV. Transmission electron microscopy was performed on Tecnai G2 F30 Twin, USA at 200 kV. Disintegration of tablets was measured using a USP disintegration tester. Drug release from the tablets was tested using a modified version of the dissolution Test 7 in the USP 39 monograph for nifedipine extended release tablets. For this study Apparatus 2 was used employing 200 mL dissolution flasks and small paddles rotating at 50 rpm. High performance liquid chromatography (HPLC, Spectrum System, AS 1000 autosampler and P2000 pump, Thermo Separation Products, Waltham, MA) equipped with a multiple wavelength UV detector was used to analyze drug concentration during release studies.

2.1. Evaluation of flow and compression properties

Prior to making measurements all powders were vacuum dried for at least 24 h. Angle of repose measurements were made by allowing powder samples to fall freely from a height of 45 mm onto a constant base with a diameter of 40 mm, through a glass funnel. The angle of repose was determined by taking photographs of the powder mound and measuring the angle formed between the horizontal surface of the base and the incline using ImageJ picture editing software. Hausner ratio and Carr's index for each sample was determined as described previously (Strydom et al., 2011).

To measure tensile strength and porosity, the powder samples were compacted into tablets. The tablets had a diameter of 8 mm and weighed approximately 100 mg. Each powder load in the die was kept under pressure for 30 s before the pressure was removed. Six different compaction forces: 60, 120, 180, 240, 300 and 360 MPa were used. Before compaction, the powders were dried under vacuum for at least 24 h and afterwards the tablets were allowed to undergo relaxation for 12 h before the tablet weight and