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Design and validation study of a laboratory scale chemical reactor for non-invasive imaging of macro objects in situ

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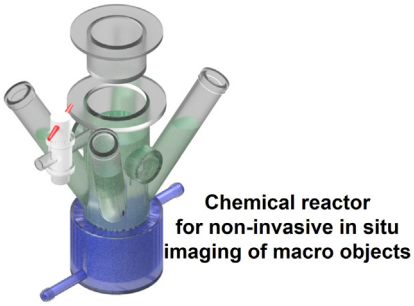
HIGHLIGHTS

- A chemical reactor is designed for optical in situ imaging of macro objects.
- Reactor design allows for agitation, probe mounting and temperature control.
- Setup is evaluated by imaging a USAF 1951 resolution chart.
- Setup is validated by imaging conformational changes in hydrogels over time.
- Principles are applicable to any non-invasive imaging of a macro object in a reactor.

GRAPHICAL ABSTRACT



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ABSTRACT

Inexpensive in situ monitoring of a conformational change in a macro object over long periods of time in a chemical reactor is challenging. One research area which would benefit from improvements in screening methods is the study of smart hydrogels, particularly when they are intended as oral forms for drug delivery or as multifunctional scaffolds replacing surgically removed tissues. Smart materials have the ability to alter their volume by swelling and/or collapsing in response to a specific stimulus in their environment. Conventional methods used to record this change such as gravimetric analysis, are invasive, require manpower for time-consuming hydrogel handling and often result in material fragmentation leading to inaccuracy. In this work, a novel reactor design is implemented in combination with inexpensive optics to achieve a non-invasive method that can be used reliably over long periods of time. Optical quality flat glass windows are incorporated in a jacketed reactor vessel design to enable undistorted imaging. The reactor was made from a chemical engineering viewpoint to enable temperature control, continuous stirring and sampling while preventing evaporative loss of solvent. Image resolution was measured using a USAF 1951 resolution test target. The setup was validated using pH responsive PVP-Chitosan hydrogels to demonstrate the capabilities of the method in monitoring the change in volume of the responsive hydrogel with time.

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1. Introduction

Chemical reactors are designed to optimise the chemical process taking place inside them. Temperature control, mixing and process monitoring are frequently required for process optimisation and control. In such cases the reactor incorporates a heating/cooling jacket, internal heater, stirrer and ports for sampling or probe mounting. The design of the chemical reactor must be capable of adapting as the requirements of the reaction system change [1]. The objective of this work is the design and validation of a lab-scale reactor for non-invasive in situ monitoring of changes in the size of a macro object over longer periods of time, e.g. hours, days, weeks. This is particularly needed in the study of smart hydrogels. Smart hydrogels are soft materials that can reversibly respond to changes in a variety of chemical and/or physical stimuli in their environment by adjusting their conformation i.e. changing volume via swelling and deswelling actions [2,3]. These materials have attracted significant scientific interest since their discovery and are quickly progressing from proof of principle to applications in the areas of drug delivery, tissue engineering, biosensors, microfluidic devices and purification systems [4–14]. At all stages of development research, endeavours require measurements of conformational change, and various qualitative and quantitative methods have been pursued. Qualitative assessment is the reporting of general observations often accompanied by an example image of a sample [15]. Quantitative methods tend to report sample size (length, radius, and thickness) measured with a ruler or Vernier calliper, or the mass of a sample measured gravimetrically [16–18]. While all of these methods are useful, each has shortfalls. Visual observations are subjective, may be inconsistent and are difficult to compare between different laboratories. Measurement of size with rulers/callipers as well as gravimetrically requires sample handling which generates inaccuracy. Smart hydrogels predominantly consist of water and therefore have a soft structure. During the handling process some of this water may be lost and some fracturing or fragmentation of the hydrogel may occur, introducing errors in measurement. Furthermore, all of these methods require human intervention and therefore are not ideal when lengthy monitoring periods are required.

In an attempt to resolve the aforementioned issues, optical methods have been introduced employing cameras and microscopes supported by digital image processing software [15,19,20]. While optical studies have led to progress in hydrogel imaging, in situ monitoring still faces limitations, in particular when lengthy screening in controlled conditions is needed. Additionally, samples are three-dimensional objects requiring imaging from multiple angles in order to reconstruct the actual size of the object and subsequent changes in size/volume. Also, containers used to store and study samples are typically made of curved glass which introduces image distortion when filled with a liquid.

This paper presents a lab-scale reactor which has been designed to enable the imaging of simple three dimensional objects over long periods of time in a controlled reaction environment. Various aspects of the prospective chemical processes were considered and the reactor was designed accordingly. A 1951 USAF resolution test target was used to test the resolving power of optical imaging while a pH responsive PVP-chitosan hydrogel was imaged as an example of an object whose change in volume requires screening over long periods of time.

2. Materials and methods

2.1. Hydrogel synthesis

Poly (vinyl pyrrolidone) (PVP) Mw 40,000 g/mol; chitosan (Cht) Mw 190,000–300,000 g/mol with 80% deacetylation; genipin (Gen) $\geq$ 98%; and glacial acetic acid were purchased from Sigma Aldrich. Glycine (pH 2) and phosphate (pH 7) buffers were obtained from Fisher Scientific. All chemicals were used as received. Cht was dissolved in an aqueous 1% (v/v) acetic acid solution with the aid of stirring at room temperature to attain a 1.5% (w/v) solution. A 5% (w/v) homogeneous transparent PVP solution was obtained by dissolving PVP in deionised water at room temperature. A transparent Gen solution 0.5% (w/v) was obtained by dissolving Gen powder in deionised water at room temperature. Two sets of hydrogel samples were prepared in polyethylene vials (Ø1 cm). The first combined 0.5 mL chitosan solution and 0.1 mL genipin solution with 0.5 mL PVP solution. The second combined 0.3 mL chitosan solution and 0.05 mL genipin solution with 0.1 mL PVP solution. In both cases mixtures were stirred for 5 min using a magnetic stirrer. Subsequently, the vials were closed and the samples polymerized at 37 °C in an oven for 24 h. Following polymerization, samples were removed from the vials and stored in pH 7 buffer to contract prior to optical study.

2.2. Optical experimentation

The optical studies reported employed the setup shown in Fig. 1. The setup consists of a breadboard with mounts, a jacketed reactor especially designed for optical screening, two Nikon cameras (models 5100 and 7000) with AF-S Micro-Nikkor 105 mm 1:2.8 G Nikon lenses, a water bath, a Pt100 temperature probe, a pH probe connected to a PC, additional lighting, and a magnetic stirrer. Note especially that a Nikon micro lens of comparatively long focal length was used (other manufactures term such a lens a macro lens). A micro lens is essential for resolving small features up close. While shorter focal length micro lenses are available at less expense, the longer focal length allows for additional freedom in the distance of the camera from the reactor. This lens, which is capable of 1 to 1 imaging, has a focal range of 0.314 m to infinity. On a DX format camera the maximum angular field of view is 15 degrees according to specifications from the manufacturer.

2.2.1. Optical reactor design

The reactor was designed (Fig. 2) and manufactured in-house (Fig. 3). To achieve a functional reactor vessel suitable for optical screening the following elements were incorporated in the design: two parallel windows on opposite sides of the reactor made form optical grade glass (Ø3 cm) for horizontal viewing; one window (Ø4 cm) made form optical grade glass incorporated in the reactor lid to enable vertical viewing; an inverted lid to allow the optical window to be immersed into the solution in the reactor to avoid issues with condensation when operating the system over longer periods of time or when running the system at elevated temperatures; a reactor jacket so that temperature can be controlled; four ports for sampling and/or probe insertion; an overflow valve to enable continuous operation when such a configuration is required.

2.2.2. Resolving power of optical setup

The resolution of the imaging system was evaluated using the 1951 USAF resolution test target. The details of the USAF 1951 resolution chart can be found in the reference [21]. However, for practical purposes consult the catalogue of virtually any supplier of research-grade optics such as Thorlabs or Edmund Optics. This resolution test target (Fig. 4a) consists of a number of pairs of three horizontal and three vertical lines ranging in size (Fig. 4b). A single pair of horizontal and vertical lines is called an element (numbered from 1 to 6) with several elements forming a group (numbered from −2 to 9). When viewing an image, the two numbers corresponding with the smallest distinguishable line pair are noted