Characteristic of Starch-Poly(N-Vinyl-Pyrrolidone) for an encapsulation material in floating drug delivery system

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Abstract. Modified starch has been widely used in many studies in the field of drug delivery for gastrointestinal drug release. In this study, the starch was modified with poly(N-vinylpyrrolidone) by interpenetrating polymer network (IPN) method. Characterizations were done to observe its characteristics in floating drug delivery applications. Three modified starch-based hydrogels were synthesized, i.e. crosslinked starch, semi-IPN, and full-IPN hydrogels. Non-modified starch hydrogel was also synthesized for benchmark purpose. All materials were characterized and analysed by Swelling Test, Buoyancy Test, Differential Scanning Calorimetry (DSC), Thermal Gravimetric Analysis (TGA), and Fourier Transform Infrared Spectroscopy (FTIR). Swelling test showed that the crosslinked-starch hydrogel has the lowest swelling percentage compared to other hydrogels, whereas non-modified hydrogels tend to have similar swelling percentage to Semi-IPN. Morphology and visual analysis results showed that non-modified hydrogels were physically the most fragile, followed by a crosslinked-starch, semi-IPN-starch, and full-IPN-starch hydrogel. Therefore, full-IPN-starch hydrogel had the highest elasticity. From IR spectrum result, it can be seen that a wavenumbers shift was observed for the modified starch compared with the IR spectrum of pure starch powder. TGA and DSC characterizations showed the degradation temperature for non-modified hydrogel was at 250°C. The degradation temperature for both crosslinked and semi-IPN starch were at 275°C. For full-IPN, however, the degradation temperature was at 225°C. On the other hand, the degradation level could be observed from DSC and TGA results as well. Full-IPN appeared to be the slowest, while non-modified hydrogel seem to be the fastest to degrade. CaCO₃ was used as the pore forming agent (PFA) in this research for buoyancy characterization. Buoyancy test showed that the full-IPN had the fastest floating lag and longest floating time followed by semi-IPN-starch, crosslinked-starch, and non-modified starch. From all characterizations done in this research, it can be suggested that the full-IPN provided the most suitable characteristics as an encapsulation material candidate in a floating drug delivery system.

1. Introduction

Biomaterial for encapsulation in drug delivery system is increasingly developed this days, i.e. carbohydrate based material, biopolymer, and modified carbohydrate based hydrogel and many more. Biopolymer hydrogel is developed as an encapsulant in the drug delivery system to delay the metabolism process, therefore, the interaction with water in the body can be slowed. It means that the drug will be slowly released and can be absorbed optimally in the body [1].

Hydrogel expands as it absorbs water or solvent, and retains their mechanical stability. Even though the levels of water or solvent absorbed in the hydrogel reached 99%, it will keep its shape and characteristics as a solid material. Therefore, hydrogel can maintain its structure with low or high

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water or solvent content in it. Chemically crosslinked methods is a versatile route to create a hydrogel with a better degree of mechanical stability [2]. Interpenetrating polymer network hydrogel (semi and full) provides additional strength and new properties for drug delivery system [3]. These hydrogels are widely used for drug delivery on a specific target (site-specific) [4], such as colon [5], and intestine [6]. Floating drug delivery system, in principle, is used to deliver drugs that are absorbed in the stomach. This carrier will absorb the water content in the stomach, therefore, it will inflate and float in the stomach. During this absorption, the drug in hydrogel will be released gradually in to the body. This method is used, so that the drug will be absorbed optimally and effectively over a time interval of metabolism in the stomach before entering the intestinal system [7]. With this system, the function of the drug could be optimized even in low doses as it increases the absorption effectiveness in the body [8].

2. Experimental

2.1. Preparation of starch hydrogels

For this experiment, several floating hydrogels were synthesized i.e. non-modified, crosslinked, semi-IPN, and full-IPN starch hydrogels. Non-modified starch hydrogel was synthesized by adding 2 grams of starch powder into 70 ml hot distillate water (80 – 90°C), then cooled down to room temperature. To synthesize the crosslinked-starch hydrogel, 2% of acetaldehyde 0.1 M was added to hydrogel solution and stirred for 3 hours. Crosslinked-starch hydrogel was added 90:10% w/w of poly( N-vinyl-pyrrolidone) and stirred in 1 hour to synthesized Semi-IPN hydrogel. Full-IPN had the most complex synthesis steps. The first step is similar as the process for crosslinked starch hydrogel, and then put in polymerization reactor with nitrogen gas condition at 70°C. The process was then continued by adding 90:10% w/w of N-vinyl-pyrrolidone in crosslinked starch hydrogel, ammonium persulfate, and N,N'-N,N'-methylene-bis-acrylamide under reflux. This solution was stirred for 1 hour. To synthesize the floating hydrogel, 1.00% calcium carbonate was added to each hydrogel solutions as pore forming agent. The solutions was stirred to ensure no air bubbles formed in solutions. All hydrogel solutions were dried in an oven at 60°C for 18 hours. [9]

2.2. Swelling ratio measurements

Swelling ratio measurements were done for floating and non-floating hydrogels. Dried hydrogels were immersed in pH 1.2 buffer solution at room temperature. For non-floating hydrogels, measurement were done in 30, 60, and 180 minutes [10]. On the other hand, floating hydrogels were measured only in 60 minutes. Filter paper is used to remove excess water on the surface of hydrogels. The swelling ratio percentage was the determined using equation 1.

\[
Swelling\ ratio\ (\%) = \left[ \frac{W_t - W_0}{W_0} \right] \times 100\ %
\]

Where \( W_0 \) is the initial weight of samples and \( W_t \) is the weight of swollen hydrogel at predetermined time (t).

2.3. In vitro buoyancy observations

The floating properties was analysed with 50 ml of pH 1.2 buffer solution at 37°C. The time required for hydrogels to rise to the surface and float (floating lag time), and the time required for hydrogel started to sink back (floating time) was measured by visual observation [11].

2.4. Physical characterizations

Differential Scanning Calorimetry (DSC) and Thermal Gravimetric Analysis (TGA) were done for physical characterizations of the hydrogels on PerkinElmer STA 6000. The test was done under temperature ranging from 50 – 500°C. Fourier Transform Infrared Spectroscopy (FTIR) was used
within the range $400 - 4000 \text{ cm}^{-1}$ on IRPrestige-21 Shimadzu. Morphology of all hydrogel was observed by Stereo-inverter microscope from Olympus SZX16.

3. Results and discussion
Morphology of hydrogel as shown in Figure 1 indicated that floating hydrogels had more pores in their surface than non-floating hydrogels. It’s also indicated non-modified starch hydrogel had the roughest surface, followed by a crosslinked starch, semi-IPN starch, and full-IPN starch hydrogel. The rough surface of hydrogels can cause fragility to the material [12]. Therefore, full-IPN-starch hydrogel had the highest elasticity.

![Figure 1. Microscope stereo-inverter scanning of non-floating hydrogels (left) and floating hydrogel (right): (a) Non-modified starch hydrogel (b) Crosslinked starch hydrogel (c) Semi-IPN starch hydrogel (d) Full-IPN starch hydrogel.](image)

The result of swelling study of hydrogels showed that, in general, swelling value increased proportionally with the duration of immersion for non-floating hydrogels (Figure 2a). The highest swelling ratio was achieved at 30, 60, and 180 minutes immersion for full-IPN, non-modified, and semi-IPN starch hydrogel respectively. Floating hydrogels, however, it was observed that floating method affect the swelling ratio as shown in Figure 2b. The swelling percentage of floating hydrogels were significantly lower than non-floating hydrogel. It might be because of pores formation in the floating hydrogel which reduce the ability of the hydrogel to absorb water.

![Figure 2. Results on swelling properties observation of hydrogels: (a). Non floating hydrogel in various time (b). Comparison between non floating hydrogel to floating hydrogel with 1.00% CaCO$_3$.](image)

The buoyancy tests showed that pores formation gave the buoyancy characteristics for the hydrogels. Non-floating starch hydrogels were not floating due to the absence of the pore. Full-IPN starch hydrogel had the fastest floating lag time followed by semi-IPN starch, crosslinked starch and non-modified starch hydrogel. The floating properties were related to gas content of polymer network [13], showed in table 1.
Table 1. Floating lag and floating time for non-floating hydrogel (CaCO₃ 0%) and floating hydrogel (CaCO₃ 1.00%)

| Hydrogel – PFA               | Floating Lag Time                      | Floating Time        |
|-----------------------------|----------------------------------------|----------------------|
| NK-CaCO₃ 0%                 | No Floating activity                    | No Floating activity |
| NK-CaCO₃ 1,00%              | 42 minutes 56 seconds                   | > 3 hours (180 minutes) |
| Crosslinked-CaCO₃ 0%       | No Floating activity                    | No Floating activity |
| Crosslinked-CaCO₃ 1,00%    | 32 minutes 39 seconds                   | > 3 hours (180 minutes) |
| Semi-IPN-CaCO₃ 0%          | No Floating activity                    | No Floating activity |
| Semi-IPN-CaCO₃ 1,00%       | 21 minutes 53 seconds                   | > 3 hours (180 minutes) |
| Full-IPN-CaCO₃ 0%          | No Floating activity                    | No Floating activity |
| Full-IPN-CaCO₃ 1,00%       | 18 minutes 21 seconds                   | > 3 hours (180 minutes) |

FT-IR spectrum of non-floating hydrogels (Figure 3a) shown that there were interaction between starch and crosslinking agent, and also PVP. This was indicated by band shifting if compared to starch powder spectrum. Starch spectrum showed O-H band at 3550 – 3000 cm⁻¹, C-H band at 2750 – 3000 cm⁻¹ and C-O band at 1250 – 1000 cm⁻¹. Floating hydrogel spectrum (Figure 3b) has shifting band compare to non-floating hydrogel. O-H band from non-floating hydrogel spectrum at 3629 cm⁻¹ to 3566 cm⁻¹. The peak at around 2900 cm⁻¹ of C-H band for floating hydrogels were stretching compared to non-floating hydrogels. The absorption band of non-floating hydrogel at around 1700 cm⁻¹ has shifted to at around 1600 cm⁻¹. This indicated that the C-OH, might be caused by formation of bonds with carbonyl groups [14,15].

Figure 3. FT-IR Spectrum of Hydrogels: (a) Non Floating Hydrogels compared to Starch powder (b) Floating Hydrogels.

The thermal spectrum of DSC and TGA (figure. 4) showed the thermal properties of non-floating starch hydrogels. The degradation temperature for non-modified, crosslinked, semi-IPN, and full-IPN hydrogel were roughly at 250°C, 275°C, 275°C, and 225°C respectively. Furthermore, the degradation level could be observed from DSC and TGA results as well. Full-IPN appeared to be the slowest,
while non-modified hydrogel seem to be the fastest to degrade. The decomposition temperature for non-modified starch hydrogel was at 300°C [16]. Crosslinked starch hydrogel had similar decomposition properties to non-modified starch hydrogel, but it has higher heat flow and lower decomposition temperature at 290°C, followed by semi-IPN and full-IPN starch hydrogel.

![DSC and TGA curves](image)

**Figure 4.** Thermal Curves (DSC and TGA) for Non Floating Hydrogels.

4. Conclusion

Non floating hydrogels showed better structure than floating hydrogels. However, for drug delivery purposes, floating hydrogels characteristics were more preferable. From all characterizations done in this research, it could be suggested that the full-IPN provided the most suitable characteristics as an encapsulation material candidate in a floating drug delivery system. Therefore, full-IPN floating hydrogel could be the most suitable material for drug release applications.

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