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Evaluation of kappa carrageenan as potential carrier for floating drug delivery system: Effect of pore forming agents

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ABSTRACT

Floating hydrogels were prepared from kappa carrageenan containing $CaCO_3$ and $NaHCO_3$ as pore forming agents. The effects of $CaCO_3$ and $NaHCO_3$ on hydrogel characterizations were investigated and compared. Amoxicillin trihydrate was used as a model drug. Characterizations of the hydrogels were carried out using Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD) and field emission scanning electron microscope (FESEM). As pore forming agents concentration increases, the porosity (%) and floating properties increased. $NaHCO_3$ incorporated hydrogels showed higher porosity with shorter floating lag time (FLT) than $CaCO_3$. Hydrogel which contained $CaCO_3$ exhibited better gel stability over the control and $NaHCO_3$ containing gel. Incorporation of $CaCO_3$ into kappa carrageenan hydrogel showed smoother surface gels compared to those produced with $NaHCO_3$. $CaCO_3$ also showed higher drug entrapment efficiency and sustained drug release profile than $NaHCO_3$. The results of these studies showed that, $CaCO_3$ is an effective pore forming agents in κC hydrogels preparation as compare to $NaHCO_3$. Thus, $CaCO_3$ can be an excellent pore forming agent for an effective floating drug delivery system.

1. Introduction

Despite remarkable advancements in the drug delivery system, the oral route remains the most common and convenient path for drug delivery due to easy administration. Limitations of the conventional oral drug delivery system such as fast emptying time and poor bioavailability of certain drugs due to incomplete absorption and degradation in gastrointestinal tract (GIT) cause researchers to search for alternative methods to replace the existing drug delivery system (Hoffman, 1998; Nayak, Maji, & Das, 2010; Streubel, Siepmann, & Bodmeier, 2006). Several approaches have been recommended to overcome these limitations such as floating drug delivery system (FDDS) (Narang, 2011), swelling or expanding systems, mucoadhesive systems (Dhaliwal, Jain, Singh, & Tiwary, 2008), modified-shape systems, high density system (Bardonnet, Faivre, Pugh, Piffaretti, & Falson, 2006) and other delayed gastric emptying devices. Among these systems, FDDS is an effective system to prolong the presence of the dosage form within the gastrointestinal tract (GIT) until all the drugs are completely released at the desired period of time (Prajapati, Patel, & Patel, 2008).

FDDS system is a low-density system that allows sufficient floating over the gastric fluid and remains afloat in the stomach for a prolonged time. While the system is floating on the gastric fluid, the drugs are released slowly at the desired rate and time from the system. After the drug release, the residual system is emptied from the stomach (Narang, 2011). The main features of floating drug delivery are: (a) act locally in the stomach; (b) primarily absorbed in the stomach; (c) poorly soluble at an alkaline pH; (d) have a narrow window of absorption and (e) unstable in the intestinal or colonic environment. FDDS system can be classified as effervescent and non-effervescent system (Singh & Kim, 2000).

In this study, effervescent systems were developed using calcium carbonates ($CaCO_3$) and sodium bicarbonates ($NaHCO_3$) as pore forming agents. Sustaining the drug release rate and excellent floatability of dosage form are directly related to the amount and type of pore forming agents. According Krishnan, Sasikumar, Prabhu, and Vijayaraghavan (2010), there is a direct correlation between the concentration of the pore forming agents towards the size, weight, pore size as well as the drug release kinetics of the beads. Thus choosing a suitable pore forming agents is also very essential for a controlled drug release. Recently, incorporation of natural polymers into FDDS along with pore forming agents became a novel method to control drug release. $NaHCO_3$ has regularly been used as a gas-forming agent for FDDS (Baumgarter, Kristl, Vrecer, Vodopivec, & Zorko, 2000; Chen & Park, 2000; Mandel,

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Daggy, Brodie, & Jacoby, 2000; Park, Liang, Yang, & Yang, 2001; Zaniboni, Fell, & Collett, 1995). There are also some research papers on $CaCO_3$ (Yellanki & Nerella, 2010; Sriamornsak, Sungthongjeen, & Puttipipatkhachorn, 2007; Pahwa, Bhagwan, Kumar, & Kohli, 2010) and others gas forming agents.

Kappa carrageenan is a seaweed polysaccharide category. Kappa carrageenan consists of repeating units of (1,3)-D-galactopyranose and (1,4)-3,6-anhydro-α-D-galactopyranose with certain amounts of sulphate groups at various positions (Campo, Kawano, Silva Junior, & Carvalho, 2009). Carrageenan tends to be hydrophilic due to the presence of hydroxyls and sulphate groups in carrageenan structure. As biocompatible and biodegradable biopolymer, kappa carrageenan can easily form gel. Hydrogels, which can be made thermo-intelligent and pH-sensitive, are three dimensional hydrophilic polymer matrices that are able to absorb and retain a large amount of water. Kappa-carrageenan hydrogel has the ability to reduce or eliminate toxicity in biomedical applications. According to Necas and Bartosikova (2013), the negatively charged sulphate polysaccharides, exert their inhibitory effect by interacting with the positive charges on the viruses including herpes simplex virus (HSV) and human immunodeficiency virus (HIV) or on the cell surface and thereby prevent the penetration of the virus into the host cells. For this reason, κC gel has been applied in immobilizing protein and drug for controlled drug delivery systems (Hezaveh & Muhamad, 2013; Leong et al., 2011; Muhamad et al., 2011; Palace, Fitzpatrick, Tran, Phoebe, & Norton, 1999). These advantageous properties of κC hydrogel enable them to become an excellent material for the fabrication of intelligent adsorptive materials for drug delivery applications.

The aim of this experiment was to prepare a floating drug delivery system using two different pore forming agents i.e. calcium carbonate ($CaCO_3$) and sodium bicarbonates ($NaHCO_3$). The effects of pore formation on structural stability, porosity, *in vitro* buoyancy, and drug entrapment efficiency were examined. The comparative efficacy of $CaCO_3$ and $NaHCO_3$ as pore forming agents for floating drug delivery was also determined. Amoxicillin trihydrate, a common treatment for peptic or gastric ulcers caused by *Helicobacter pylori* infection, was used as a model drug in the study (Pandit, Suresh, & Joshi, 2010).

2. Material & methods

2.1. Material

Amoxicillin trihydrate from Pusat Kesihatan UTM, Kappa-Carrageenan (κC) was purchased from Sigma-Aldrich (Malaysia), sodium carboxymethyl cellulose (NaCMC) (average molecular weight of 250,000) was purchased from Acros Organic (Malaysia), calcium carbonate ($CaCO_3$) and sodium bicarbonates ($NaHCO_3$) were purchased from Sigma-Aldrich (Malaysia). Distilled water was used in hydrogel synthesis and all chemicals were used as received with no additional purification.

2.2. Preparation of hydrogels

2.2.1. Preparation of kappa carrageenan/sodium carboxymethyl cellulose hydrogels

To enhance the swelling properties, kappa carrageenan was synthesized with different concentrations of NaCMC. Hydrogel blends were formulated with different ratios of κC:NaCMC (60:40, 70:30, 80:20 and 90:10) by mixing the hot kappa carrageenan solution with appropriate amount of NaCMC in 30 ml of distilled water at 80 °C under reflux condition. The solution was stirred for 1 h to obtain a clear, viscous and homogenous solution with no bubble.

Table 1
Synthesis condition of κC/NaCMC hydrogels and floating hydrogels containing $CaCO_3$ and $NaHCO_3$.

Sample designation	κC (g)	NaCMC (g)	$CaCO_3$/$NaHCO_3$ (g)	Water (ml)
κC60	0.36	0.24	–	30
κC70	0.42	0.18	–	30
κC80	0.48	0.12	–	30
κC90	0.54	0.06	–	30
κC80 – 0%	0.48	0.12	0	30
κC80 – 0.25%	0.48	0.12	0.08	30
κC80 – 0.5%	0.48	0.12	0.15	30
κC80 – 0.75%	0.48	0.12	0.23	30
κC80 – 1.0%	0.48	0.12	0.30	30

Then, the resultant hot solution was poured into ceramic moulds to form the hardened hydrogel of a desired shape. Samples were equilibrated at ambient temperature (25 °C) for 24 h prior to drying at 37 °C in an oven which was left overnight.

2.2.2. Measuring swelling ratio

To study the swelling properties of hydrogels, modified gels were immersed in different pH buffer solutions of pH 1.2 at room temperature (25 °C). Synthesized gels were placed in a petri dish filled with 50 ml of each buffer solution. Prior to weighting, filter paper was used to remove the surface water of swollen hydrogel. The test was conducted in triplicate and reported as mean values to maximize accuracy. The swelling ratio (%) was then determined using Eq. (1)

$$\text{Swelling ratio}\,(\%) = \left[\frac{W_t - W_0}{W_0}\right] \times 100\% \quad (1)$$

where W_0 is the initial weight of samples and W_t is the weight of swollen gels at predetermined time t. To allow hydrogels to reach their highest swelling ability, they were immersed in fresh buffer solution after weighting.

2.2.3. Preparation of amoxicillin trihydrate loaded floating hydrogel

To prepare floating hydrogel, the most suitable hydrogel blend was selected from the swelling study. Calcium carbonates and sodium bicarbonates were used as pore forming agents. Calcium carbonates with different concentrations were added to the hot solution of κC/NaCMC in 25 ml of distilled water at 80 °C under reflux. The solution was stirred to ensure no air bubbles formed in the solutions. Then, a solution was prepared by dissolving 250 mg of the drug in 5 ml distilled water and was added to the hot solution of κC/NaCMC/$CaCO_3$ at 25 °C under continuous stirring to ensure no air bubbles formed in the solutions. The homogeneous viscous solutions were kept in the moulds at room temperature (27 °C) overnight. Finally, the hydrogels were dried in an oven at 37 °C for 24 h. The same procedure was carried out to prepare floating hydrogel with sodium bicarbonates. Table 1 lists the synthesis conditions for the different hydrogels synthesized in this experiment.

2.3. Physical characterization

2.3.1. Drug entrapment efficiency

For entrapment efficiency analysis, hydrogels (250 mg) were powdered and dissolved in 10 ml of 0.1 N HCl. It was then sonicated for 1 h and diluted to 100 ml with 0.1 N HCl. It was then filtered through Whatman filter paper no. 41. Suitable dilutions were made and the filtrate was analysed spectrophotometrically at 272 nm. Triple measurements were performed for each examined