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# An investigation of effects of modification processes on physical properties and mechanism of drug release for sustaining drug release from modified rice

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ABSTRACT

The aim of this study was to investigate the effect of modification processes on physical properties and explain the mechanism of sustained drug release from modified rice (MR). Various types of Vietnamese rice were introduced in the study as the matrices of sustained release dosage form. Rice was thermally modified in water for a determined temperature at different times with a simple process. Then tablets containing MR and isradipine, the model drug, were prepared to investigate the capability of sustained drug release. Scanning electron microscopy (SEM) was used to determine different morphologies between MR formulations. Flow property of MR was analyzed by Hausner ratio and Carr's indices. The dissolution rate and swelling/erosion behaviors of tablets were evaluated at pH 1.2 and pH 6.8 at 37 ± 0.5 °C. The matrix tablet containing MR showed a sustained release as compared to the control. The SEM analyses and swelling/erosion studies indicated that the morphology as well as swelling/erosion rate of MR were modulated by modification time, drying method and incubation. It was found that the modification process was crucial because it could highly affect the granule morphologies and hence, leading to the change of flowability and swelling/erosion capacity for sustained release of drug.



## 1. Introduction

Hydrophilic polymer matrices have been widely used in formulations of sustained release (SR) systems to achieve slow release of drug over an extended period of time [1–4] due to low cost, ease of manufacture and relative independence of the physicochemical and physiological conditions of the gastrointestinal tract [5,6]. Generally, the hydrophilic polymer hydrates when it exposes to dissolution medium to form the gel layer as the barrier controlling drug release. Hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), xanthan gum, sodium alginate, poly (ethylene oxide) and crosslinked homopolymers and copolymers of acrylic acid are commonly used as hydrophilic matrices [7–11].

Rice has been widely used in food industry and direct food use [12]. Despite promising characteristics of a safe material with starch component adding up to almost 90% of milled rice [13], its application in pharmaceutical industry is still limited. Recently, starch has been considered as a promising biomaterial in pharmaceutical industry due to the unique physicochemical and functional characteristics [14–16]. Native starches have been well explored as binders and disintegrants in solid dosage forms; however, the utilization is restricted due to poor flowability. Meanwhile, modified starches have been investigated for applications of sustained release agents as hydrophilic matrices [17–21] in drug delivery systems. Starch-based biodegradable polymers used in preparation of microspheres or hydrogels have been studied for drug delivery [22,23]. Starch like rice starch could be modified by chemical, physical or enzymatic methods to have distinctive properties. Mechanism of drug release from modified rice matrices would be a result of the passage of drug molecules controlled by the matrix structure and gel layer formation.

The granular structure and swelling ability in cold water of native starches have been investigated by physical modifications such as extrusion, drum-drying and a controlled pregelatinization-spray-drying [17]. However, few studies have investigated thermal modification on physical properties and changes of drug release mechanism from modified rice in details so far. The study introduced various types of Vietnamese rice as possible carriers for sustained release of drug in a simple process with common apparatuses. The potential rice was selected for further use in investigation of effects of modifying time, incubation method, and drying method on the flow property, granule

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morphology, swelling and erosion capacity of modified rice-based tablets. Hence, dissolution profiles of tablets, analysis of flowability, SEM images as well as swelling and erosion studies were carried out in the study.

## 2. Materials and methods

### 2.1. Materials

Various types of Vietnamese rice which were harvested and packed in the same year (2014) were introduced in the study: Nep Bac (NB) from Xuan Hong company (Viet Nam), Nep Thom (NT) from Gentraco Corporation (Viet Nam), Vua Lieu (VL) from ITA Fragrant Rice Research & Export Corporation (Viet Nam), Hoa Vang (HV) from Ngoc Hoan company (Viet Nam). Rice packages were stored at room temperature (25 °C) for study. Microcrystalline cellulose (Avicel® PH 102) was purchased from Brenntag Group (Germany). Magnesium stearate (MgS) was purchased from Nitika Pharmaceutical Specialities Pvt. Ltd (India). Hydrochloric acid (HCl) and Sodium chloride (NaCl) were purchased from Xilong Chemical Industry Incorporated Company (China). Hydroxypropyl methyl cellulose 4000 (HPMC) was provided by Dow Chemical Company (USA). Polyethylene glycol (PEG) was purchased from Sino-Japan chemical (Taiwan). Methanol (MeOH) was purchased from Fisher Scientific International, Inc. (US). Monopotassium phosphate ($KH_2PO_4$) was purchased from Wako Pure Chemical Industries (Japan). Aerosil® 200 was from Jebsen & Jessen Chemicals Holding Pte Ltd (Singapore). Mannitol (Pearlitol®) was purchased from Roquette Pharma Company, France.

### 2.2. Methods

#### 2.2.1. Modification of rice

Four varieties of glutinous rice were milled and sieved by 500 μm sieve. Then, 15 g of each type of glutinous rice was dispersed in 150 mL of distilled water and incubated at 90 °C for 4 h. The swelling rice was then heated in an oven at 120 °C with different times. The mucilage was dried in the oven at 60 °C or freeze-dried at −52 °C. The modified rice (MR) was finally passed through 500 μm sieve. The detailed conditions for MR were described in Table 1.

#### 2.2.2. Preparation of prolonged release tablet

Solid dispersion of isradipine was prepared by melting method. Briefly, mixture of polymer (PEG:HPMC = 1:1) and drug at the ratio 8:1 was melted at 160 °C. Drug was dispersed in the melted polymer. Aerosil® 200 was used as a sorbent of solid dispersion (Aerosil® 200:solid dispersion = 1:3). The resultant mixture was passed through a 500 μm sieve and thoroughly mixed with MR and mannitol. Finally, MgS was blended with the above mixture which was then compressed into tablets of diameter 8mm using a single punch-press machine (TDP 1.5, China). Hardness of the tablets was controlled at 30 ± 5 N. Each 150 mg tablet contained 60 mg solid dispersion of isradipine, 20 mg MR, 68.5 mg mannitol and 1.5 mg MgS.

#### 2.2.3. Dissolution studies

The tablets were introduced to an *in vitro* dissolution test at 37 ± 0.5 °C using type II apparatus dissolution tester (DT70 Pharmatest, Germany) at 50 rpm. To evaluate capability of sustained drug release, each dissolution vessel contained 750 mL of 0.1 N hydrochloric acid (pH 1.2) for 2 h and then the pH of the medium was adjusted to pH 6.8 by adding 250 mL of 0.2 M sodium phosphate solution, preheated to 37 °C (2 M hydrochloric acid or 2 M sodium hydroxide was used for minor pH adjustment) [24]. 1 mL of sample was collected from the media at 1, 2, 6, 10, 14, 18, and 24 h. 100 μL sample solutions were diluted for HPLC test.

#### 2.2.4. High performance liquid chromatography (HPLC) analysis

The quantification of isradipine was performed using Ultimate 3000 HPMC Thermoscientific Inc., USA. The mobile phase contained Methanol:Water:Acetonitrile mixture at the ratio 46%, 20% and 34%, respectively with a flow rate of 1.00 mL/min and the running time was 4 min. The UV/VIS detector was set at a wavelength of 325 nm. 20 μL of sample was injected to HPLC system.

#### 2.2.5. Flow property test

The Carr's compressibility index and the Hausner ratio were calculated to provide a measure of the flow properties and compressibility of MR powders. However, firstly bulk and tap densities of MRs were determined before and after 1250 taps, respectively, using the tap density tester (SVM, ERWEKA GmbH, Germany).

The Hausner ratio and Carr's index was determined as follows:

$$\text{Hausner ratio} = \frac{\text{tapped density}}{\text{bulk density}} \quad (1)$$

$$\text{Carr index} = \frac{(\text{tapped density} - \text{bulk density})}{\text{tapped density}} \times 100 \quad (2)$$

#### 2.2.6. Scanning electron microscopy (SEM)

Samples were stuck onto conductive carbon adhesive tape. The morphology was then examined under the scanning electron microscope (Hitachi's S-4800 FE-SEM, Japan).

#### 2.2.7. Swelling and erosion studies

The rate of MR swelling was determined by equilibrium weight gain method [25]. Tablets were accurately weighed ($W_0$) and put in sinkers to conduct the swelling test using the USP II apparatus (50 rpm, 37 °C, and a 900 mL dissolution medium of buffer pH 1.2 and buffer pH 6.8) with a dissolution tester (DT70 Pharmatest, Germany). Sinkers of tablets were carefully removed from the media after 1, 2 and 6 h and the tablets were lightly blotted with tissue paper to remove excess surface water and then reweighed ($W_t$). The percent water uptake or swelling rate due to absorbed liquid was estimated at each time point using

**Table 1**
Method of rice-based tablet formulations.

| Formulation | Modified temperature (°C) | Modifying time (h) | Incubation time (h) | Type of rice | Drying method | Code |
|---|---|---|---|---|---|---|
| F1 | 120 | 8 | 4 | NT | Oven at 60 °C | NT 8 h |
| F2 | 120 | 8 | 4 | NB | Oven at 60 °C | NB 8 h |
| F3 | 120 | 8 | 4 | HV | Oven at 60 °C | HV 8 h |
| F4 | 120 | 8 | 4 | VL | Oven at 60 °C | VL 8 h |
| F5 | 120 | 10 | 4 | NT | Oven at 60 °C | NT 10 h |
| F6 | 120 | 12 | 4 | NT | Oven at 60 °C | NT 12 h |
| F7 | 120 | 8 | 4 | NT | Freeze-drying at −52 °C | NT 8 h freeze-drying |
| F8 | 120 | 10 | 4 | NT | Freeze-drying at −52 °C | NT 10 h freeze-drying |
| F9 | 120 | 12 | 4 | NT | Freeze-drying at −52 °C | NT 12 h freeze-drying |
| F10 | 120 | 8 | 0 | NT | Oven at 60 °C | NT 8 h without incubation |