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# Investigation of the potential application of sodium bentonite as an excipient in formulation of sustained release tablets

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ABSTRACT

In this study, the application of sodium bentonite (SB) in formulation of tablets prepared by direct compression for oral administration was tested. Three different model drugs with different solubilities: paracetamol, diclofenac sodium and metformin HCl were tested. Each drug was mixed with SB at ratio of 50% and the mixtures were subsequently compressed. Compatibility studies were conducted using both Deferential Scanning Calorimeter (DSC) and Fourier Transform Infrared Spectroscopy (FTIR). The dissolution profile for each drug was determined in USP-buffers at different time intervals. Diclofenac sodium in pH 6.8 buffer and paracetamol in both pH 6.8 and pH 4.5 buffers showed extended release. However, metformin HCl showed immediate release at the different pH values. The study showed that using SB was possible to prepare tablets with different release profiles. However, these profiles differ depending on dissolution media and drug type.



## 1. Introduction

European pharmacopeia (2003) defined bentonite as a naturally occurring mineral clay consisting mainly of montmorillonite which is a hydrated aluminum silicate $Al_2O_3\_4SiO_2\_H_2O$ and can swell with a little water forming a malleable mass [1]. Sodium bentonite (SB) is generally prepared via activation of bentonite using sodium carbonate ($Na_2CO_3$) [2,3]. The hydrated aluminum silicates are not absorbed into the systemic circulation, and so bentonite is considered safe for oral delivery [4,5]. Moreover, according to part 184 (direct food substances affirmed as generally recognized as safe) in federal code of regulation 21 of American FDA, bentonite can be used in pure form and it would be suitable for its intended use in food with no limitation. Bentonite has been applied as an adsorbent for toxic

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materials due to the reactivity of montmorillonite [6]. It has been also used to remove contaminants from water [7].

However, few studies have concentrated on using bentonite as an excipient for preparing of tablets. Bai et al. [8] used bentonite as a disintegrant agent to prepare dispersible ibuprofen tablets. The study showed a fast dissolution rate of the prepared ibuprofen tablets. In a study by Lin et al. [9], montmorillonite was intercalated with 5 fluorouracil to produce a composite of 5 fluorouracil/montmorillonite which is expected to be used to treat colorectal cancer. Also, ranitidine intercalated with montmorillonite has been prepared by ion-exchange process. These prepared intercalated particles were further coated with Eudragit. The release profile showed that ranitidine is released in a controlled manner [10].

Bounabi et al [11] showed that clay sheets of sodium montmorillonite acted as effective multifunctional cross-linkers when 2-hydroxyethyl methacrylate monomer has been intercalated into the interlayer spaces of sodium montmorillonite (MMT) nanoparticles.

In tableting, tablets are produced by three main techniques; wet granulation, dry granulation and direct compression [12]. Each of these techniques has its merits and demerits. Direct compression is considered the technique of choice for producing tablets which contain thermo sensitive materials [13]. The main advantages of using direct compression are the shorter processing time, less energy consumption, overcoming the stability problems associated with thermolabile materials, less excipient used, and for some compounds the dissolution rate is faster compared to those prepared by wet or dry granulation [14]. However, some of the demerits include segregation, cost, low dilution potential, lubricant sensitivity and variation in functionality [14,15].

This study aims to investigate potentials of using SB as an excipient in direct compression of 50% SB tablets containing three different drugs with different solubilities: paracetamol, diclofenac sodium and Metformin HCl. The dissolution profile for each drug was measured in pH 1.2, 4.5 and 6.8 dissolution media which represent different physiologic pH. In addition, the flowability, hardness, friability and weight uniformity were measured. Moreover, DSC and FTIR-spectra for the different mixtures were measured to detect any possible interaction between the drugs and SB.

## 2. Materials and methods

### 2.1. Materials

Paracetamol was purchased from Zhejiang Kangle pharmaceutical (Wenzhou Zhejiang, China) while diclofenac sodium was purchased from Amoli Organic (Mumbai Maharashtra, India). Metformin HCl was purchased from Wanbury (Navi Mumbai, India). Sodium bentonite was purchased from Alfa Aesar (Ward Hill, MA 01836, USA). Sodium hydroxide, acetic acid, sodium acetate and $KH_2PO_4$ were all purchased from Merck (Darmstadt, Germany). HPLC grade of methanol and acetonitrile were purchased from Full time (China) while tetrahydrofuran (HPLC grade) was purchased from Labchem (Zelienople, PA 16063, USA).

### 2.2. Methods

#### 2.2.1. Preparation of powder and direct compression

Paracetamol, diclofenac sodium and metformin hydrochloride powders were sieved separately through a 45 μm sieve. Each powder then mixed with SB at ratio of 1:1, and the mixtures were then compacted by direct compression using Erweka AR 400E (Heusenstamm, Germany) to produce paracetamol, diclofenac sodium and metformin hydrochloride tablets. The weight and hardness of the tablets were adjusted to be 500 mg and 145 ± 10 newton respectively. The die was filled manually to adjust the weight of produced tablets accurately.

#### 2.2.2. Flowability measurement

The volume of 10 g of each powder was measured using a 25 ml cylinder to determine bulk density. Then the cylinder was tapped 100 times for estimation of tapped density. Three replicate measurements were performed according to the guideline stated in United States Pharmacopeia 34 (USP 34) [16].Carr's index (CI) and Hausner Ratio (HR) were subsequently calculated according to the following equations:

$$CI = \frac{Tapped\ density - Bulk\ density}{Tappeddensity} * 100 \quad (1)$$

$$Hausner\ Ratio = \frac{Tapped\ density}{Bulk\ density} \quad (2)$$

#### 2.2.3. Friability measurement

Friability testing was conducted according to the USP34 pharmacopeia. Briefly, 10 tablets were weighed and transferred to friability tester (Erweka TAR20, Heusenstamm, Germany). The apparatus was operated at 40 radius per minute for 2.5 min. The tablets were removed, de-dusted and re-weighed accurately. The percent friability was calculated using the following equation.

$$\%Friability = [(W_I - W_F)/W_I] \times 100$$

Where, $W_I$ is the initial weight of the tablets and $W_F$ is their weight after friability test.

#### 2.2.4. Hardness measurement

The hardness of the tablets was monitored using Erweka TBH30 (Germany).

#### 2.2.5. Differential scanning calorimeter (DSC) measurements

The DSC thermograms of the active pharmaceutical ingredients and their physical mixtures with SB were recorded using diffraction scanning calorimeter (DSC 204 F1 phoenix instrument (Netzsch-Gerätebau GmbH, Postfach, Germany). Their measurements were taken between 25 and 350 °C at a heating rate of 10 °C/min under dry nitrogen flow of 20 ml/min. The DSC thermograms were recorded in triplicate. DSC calibration was performed using indium (10 mg, 99.999 % pure, melting point 156.60 °C, heat of fusion 28.40 J/g).

#### 2.2.6. Fourier transform infrared spectroscopy (FTIR) measurements

The compatibility between different drugs and SB was evaluated by recording of spectra using FT-IR spectrometer (Perkin