Formulation and release kinetics of ibuprofen/bentonite tablets

Jamal Alyoussef Alkrad[1*], Sindus Sammarraie[1], Eman Zmaily Dahmash[2], Nidal A. Qinna[3], Abdallah Y Naser[1]

[1]*Faculty of Pharmacy, Department of Applied Pharmaceutical Sciences and Clinical Pharmacy, Isra University, PO Box 22 and 23, Amman, Jordan.*
[2]*School of Life Sciences, Pharmacy and Chemistry, Department of Chemical and Pharmaceutical Sciences, Kingston University, KT1 2EE, London, United Kingdom*
[3]*University of Petra Pharmaceutical Center (UPPC), Faculty of Pharmacy and Medical Sciences, University of Petra, PO Box 961344 Amman 11196, Jordan*

Running head: Development of bentonite-based sustained release ibuprofen tablets

*Corresponding author:
Jamal Alyoussef Alkrad, Faculty of Pharmacy. Isra University. Tel: 00962789696157, Fax: 0096264711505. Amman Jordan PO Box 22 and 23, Amman, Jordan. E-mail: jamal.alkrad@iu.edu.jo

This is a 'preproof' accepted article for Clay Minerals. This version may be subject to change during the production process.
DOI: 10.1180/clm.2022.35

ABSTRACT

Bentonite-based formulations offer several advantages, including being biocompatible and cost-effective, and can be used to develop gel-like matrices that provide potential for use in sustained-release formulations. Developing a high-load sustained-release formulation was reported to be challenging; therefore, the aim of this study was to systematically develop bentonite-based sustained-release tablets for a high-load active (ibuprofen) and investigate their release kinetics. Ibuprofen-loaded tablets (800 mg) were prepared using wet and dry granulation followed by enteric coating of the tablets. Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray powder diffraction (XRD) were used to evaluate the compatibility of ibuprofen with bentonite. The results showed that tablets complied with the compendial requirements. In addition, the release profile of the formulations revealed that the drug followed a non-Fickian release model. The present formulation demonstrates the new use of bentonite as a safe and cost-effective excipient with adequate binding and compaction for preparing sustained-release tablets.

KEYWORDS: bentonite; ibuprofen; granulation; binder; sustained release; tablets.

INTRODUCTION

The European pharmacopeia defined bentonite as a natural clay containing a high proportion of montmorillonite, a native hydrated aluminum silicate in which some aluminum and silicon atoms can be replaced by other atoms, such as magnesium and iron (Council of Europe, 2003). Bentonite is practically insoluble in water but swells to approximately 12 times its original volume to produce viscous, homogeneous suspensions or gels, depending on its concentration (Council of Europe, 2003; Gattermann et al., 2001; Gökalp et al., 2011; Nutting, 1943; USP-35, 2011). Montmorillonite, which is the main component of bentonite, consists of layers of negatively charged sheets held together by charge-balancing counter ions such as Na^{+} and Ca^{2+}. These cations have the propensity to

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

be hydrated in the presence of water pushing the layers away from each other in a series of discrete steps (Boek et al., 1995; Van Olphen, 1953). The hydrated aluminum silicates are not absorbable into blood (Sharma et al., 2014; Willhite et al., 2012), and according to Section 184.1155 in the federal code of regulation 21 of the American Food and Drug Administration (FDA), bentonite is considered safe and can be added in pure form and is appropriate for its intended use in food without limitation (FDA, 2021).

Bentonite has found its way into many pharmaceutical and biomedical applications, such as improving organoleptic qualities, solubility, and stability and protecting the skin from external physical harm (Hun Kim et al., 2016).

Many challenges associated with oral drug delivery systems can be resolved by formulating modified-release or targeted-release dosage forms (Agarwal et al., 2017; Bechgaard & Nielsen, 1978; Chen et al., 2010). The development of sustained release formulations involves several challenges related to the cost of polymers, the complexity of the process, drug dumping, and loading capacity (Chen et al., 2010; Wen & Park, 2011). Therefore, simple and cost-effective alternative strategies are needed.

Gel-forming hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) are commonly employed in preparing sustained-release tablets (Cao et al., 2013; Chakraborty et al., 2009; Gao et al., 1995). The viscosity of cellulose derivatives such as HPMC varies depending on the degree of substitution. Furthermore, their solubility and gelation are temperature dependent. The gel-forming polymers swell in the presence of water, where a large quantity of the drug can be immediately released. Therefore, sustained release behavior may be compromised (Ghosal et al., 2011).

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

In addition, the increase in stomach pH can decrease the stomach emptying time (Chaw et al., 2001), which improves the patient's compliance by reducing the residence time of the drugs in the stomach. The expected reduction in residence time can reduce the irritating effect of these drugs on the stomach. However, employing bentonite in the development of high-load drugs, such as ibuprofen, in enteric-coated sustained-release tablets was not previously explored.

Bentonite as a gel-forming matrix system is considered less expensive than other gel-forming polymers, including HPMC. The use of clay minerals such as bentonite and kaolinite in developing sustained release dosage forms has been reported by many studies (Alkrad et al., 2017; Li et al., 2021). The basic pH of bentonite makes it favorable to improve the absorption of class II drugs, such as ibuprofen (IB), by enhancing their solubility (Tantishaiyakul, 2004). In addition, the increase in stomach pH can decrease the stomach emptying time (Chaw et al., 2001), which improves the patient's compliance by reducing the residence time of the drugs in the stomach. The expected reduction in residence time can reduce the irritating effect of these drugs on the stomach. However, employing bentonite in the development of high-load drugs, such as ibuprofen, in enteric-coated sustained-release tablets was not previously explored.

Owing to the added value of bentonite characterized by its known biocompatibility, safety profile, cost-effectiveness, and potential for patient compliance, this study aimed to investigate the use of bentonite for preparing compendial sustained release 800 mg ibuprofen tablets as a high dosing drug by employing a multiparticulate system made of bentonite matrix and studying the release kinetics of the drug from the developed tablets.

MATERIALS

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

Ibuprofen (IB) was a generous gift from the United Pharmaceuticals Company Ltd. (Amman, Jordan). Methanol and acetonitrile (HPLC grade) were purchased from Honeywell Research Chemicals (Seelze, Germany). Microcrystalline cellulose (MCC) (Avicel®102) was purchased from FMC Corporation (Brussels, Belgium). Monobasic dihydrophosphate (KH_2PO_4) and magnesium stearate were purchased from Scharlau Chemicals (Barcelona, Spain). Pharmaceutical grade bentonite (sodium-calcium bentonite), polyvinylpyrrolidone (PVP-40T), and polyethylene glycol 4000 (PEG-4000) were purchased from Sigma–Aldrich (Steinheim, Germany). Sodium hydroxide, glacial acetic acid and sodium acetate were purchased from Merck (Darmstadt, Germany).

EXPERIMENTAL

Granulation and tableting

Ibuprofen (IB) powder was sieved through a 45-µm sieve after milling using a mortar and pestle. The required amounts of bentonite, binder, and IB were weighed and mixed thoroughly using a mortar and pestle. Three binders were investigated, including MCC (5%-10%), PEG-4000 (5%-10%), and starch (10%). Moreover, tablets without binders were prepared. Hydroxypropyl methylcellulose (HPMC) is a gel-forming binder, and polymers commonly used in formulating sustained-release tablets were excluded in this study to avoid any influence on the results (Cao et al., 2013; Gao et al., 1995; Ghosal et al., 2011). The amount of each component was calculated based on a final tablet weight of 1400 mg containing a constant amount of IB (800 mg). Magnesium stearate was mixed with granules as a lubricant with a concentration of 1% w/w. Table 1 presents the percentage (w/w) of each ingredient.

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

Table 1. Summary of the composition of different ibuprofen-loaded extended-release tablets

Formulation	IB (mg)	Bentonite (mg)	Binder Type	Binder mg (%w/w)	Lubricant (mg)	Tablet weight (mg)
IB-MCC5	800	516	MCC	70 (5%)	14	1400
IB-MCC10	800	446	MCC	140 (10%)	14	1400
IB-W	800	600	-	-	14	1400
IB-PEG5	800	516	PEG 4000	70 (5%)	14	1400
IB-PEG10	800	446	PEG 4000	140 (10%)	14	1400
IB-MCC10dry	800	446	MCC	140 (10%)	14	1400
IB-starch10	800	446	Starch	140 (10%)	14	1400

Wet granulation

The powder blend was sprayed with a sufficient amount of granulating liquid (water) for wet massing. Then, the wet mass was forced through a 350 µm sieve to form the granules. The obtained granules were placed on a stainless-steel tray and dried in a hot air oven at 56 °C for 12-14 hrs. Finally, the dry granules were passed through a 250 µm sieve.

Dry granulation

The large tablets were prepared from a mixture of IB and MCC milled using a mortar and pestle and then passed through a sieve with an aperture size of 355 µm. The prepared granules were mixed with 1% magnesium stearate before manual compression in a 13 mm die for IB tablets using an AR 400E single punch tableting machine made by Erweka (Heusenstamm, Germany).

Granule flowability measurement

A volume of 20 g of the prepared granules was estimated using a 25 mL measuring cylinder. The powder volume was taken using the same measuring cylinder after tapping the cylinder 50 times or until a fixed volume was attained. The bulk density of the powder was calculated by dividing the weight of the powder by its volume, whereas the tapped

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

density was calculated by dividing the weight of the powder by its volume after tapping. Three replicated measurements were made following the guidelines of the US pharmacopoeia (USP-35, 2011). Carr's compressibility index (CI) and Hausner ratio (HR) were calculated according to Eq. 1 and Eq. 2) (USP-35, 2011)

$$CI = \left[\frac{Tapped\ density - Bulk\ density}{Tapped\ density}\right] * 100 \quad (1)$$

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

Measuring friability

The friability of the prepared tablets was determined using 10 tablets of IB. Tablets were weighed accurately before placing them in the friability tester (Erweka TAR20, Heusenstamm, Germany). The device was set at 25 rpm for 4 min. The discs were removed, and the tablets were accurately reweighed after dedusting and careful evaluation of their integrity. Friability was calculated using Eq. 3 (USP-35, 2011).

$$Friability\ (\%) = \frac{W_I - W_F}{W_I} \quad (3)$$

where W_I is the initial weight of the tablets and W_F is their weight after the friability test.

Measurement of tablet hardness

The hardness of the prepared tablets was measured using an Erweka TBH30 tablet hardness tester (Heusenstamm, Germany). Each test was made for 6 tablets.

Fourier Transform Infrared Spectroscopy (FTIR) analysis

An FTIR spectrometer (PerkinElmer UATR Two, Li600301, UK) was used to predict the compatibility between IB and bentonite. The spectra of IB, bentonite, water, the physical

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

mixture of bentonite and IB, and the prepared granules (IB + bentonite) were measured between 450 and 4000 cm^{-1} to evaluate any change in the spectra after granulation or in the mixture.

Differential scanning calorimeter (DSC) measurements

A differential scanning calorimeter (Model 204 F1 Phoenix, Netzsch-Gerätebau GmbH, Germany) was used to record the thermograms of a mixture of bentonite and IB. The thermograms were measured in triplicate between 25 and 300 °C under a dry nitrogen flow of 20 mL/min at a heating rate of 10 °C/min. DSC calibration was performed by indium.

X-ray powder diffraction (XRD)

The X-ray powder diffraction (XRD) patterns of bentonite powder and the milled granules of bentonite with IB were obtained by a Schimadzu XRD-7000 diffractometer (Kyoto, Japan) equipped with graphic monochromatic CuKα radiation and a fixed power source (40 KW, 30 mA) with λ equal to 1.5406 Å. The scan rate was 0.5° (2θ) min^{-1}. The basal spacing (d_{100}) of bentonite alone or with the IB mixture was calculated using Bragg's law (Haoue et al., 2020) and Eq. 4 to assess whether the blending process caused substantial changes in the lamellar layers of the bentonite crystal structure.

$$2.d.sin\theta = n.\lambda \qquad (4)$$

where d is the calculated basal spacing (d_{001}) measured in Å, λ is the X-ray wavelength, n is the diffraction order (n=1 in the case of first order), and θ is Bragg's angle in degrees.

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

Dissolution test

The dissolution test was performed using a USP II dissolution apparatus (SR6, Hanson Research, CA, USA) by measuring the amount of drug released from the tablets over 24 hrs at a rotation speed of 50 rpm and a temperature of 37±0.1 °C. The dissolution medium was made of 900 mL of phosphate buffer (pH 7.2) (USP-35, 2011). Samples were removed (2 mL) at the following time intervals: 1, 2, 3, 4, 5, 6, 7, 8, 16, 20 and 24 hr. Samples were filtered using a 0.45 µm membrane filter before determining the amount of dissolved drug using the corresponding HPLC method.

High-performance liquid chromatography (HPLC) assay

The released drug amount was quantified by a Thermo Scientific chromatographic system (Dionex Ultimate 3000 HPLC, Germany) connected to a diode array detector. A 10 µL injection volume was separated through a 250 × 4.6 mm C8 column (Nanologica, Södertälje, Sweden). The mobile phase used to quantify IB was composed of 5 mL/L glacial acetic acid in HPLC grade water and acetonitrile (50:50). IB was pumped at a flow rate of 2 mL/min to detect IB at a wavelength of 230 nm.

Enteric coating using Eudragit®

The tablets were subcoated using Opadry-28900 (Colorcon, PA, USA). The percentage of the subcoat was 3% of the weighted tablets. A 12.5% EUDRAGIT® L 30 D-55 suspension (Evonik Rhon GmbH, Germany) was used for enteric coating of the tablets. The aqueous suspension was composed of 1% triethyl citrate (plasticizer) and 5% talc (anti-tacking) plus the polymer. The tablet coater setups were as follows: a) nozzle bore 1.2 mm, b) distance nozzle/product: 10 cm and c) internal silicone tube diameter: 2 mm. The coating was

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

performed in the HI-Coater system (Freund Vector, USA) and according to technical information of EUDRAGIT® L 30 D-55 for top spray on 1 kg of tablets (Evonik, 2021). The processing parameters were as follows: a) atomizing air pressure of 1.8 bar, b) filter rattling time of 5 s, c) filter rattling interval of 30 s, d) drying air volume of 90 m^3/h, and e) drying air capacity of 1.5 m^3/(min•kg). The inlet air temperature was set at 40 °C, the exhaust air temperature was 28 °C, the product temperature was 28 °C and the spray rate was set at 15 g/(min•kg).

Evaluation of enteric-coated tablets

Three tablets from each enteric-coated tablet type were immersed in 0.1 N HCl solution as a dissolution medium. The apparatus was run at a rate of 50 rpm and a temperature of 37±0.1 °C. A sample from each vessel was removed after two h to ensure the acidic resistance of the coating by testing if the drug was released from the coat in the acidic medium (USP-35, 2011). Then, the HCl solution was replaced by 7.2 phosphate buffer for IB, and samples were assessed for drug release over 24 h.

Release kinetic modeling and statistical evaluation

The release data of IB until 16 h (after releasing approximately 60% of the total amount of the drug) from the formulated tablets were used to find the proper model of four kinetic models by estimating the correlation coefficients (r2). The first model was the zero-order release model. This model describes the independent drug release of concentration at a constant rate from modified-release tablets. The correlation was obtained by plotting the cumulative released amount (Q) against the time (t) (Eq. 5) (Dash et al., 2010;

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

"Mathematical Models of Drug Release," 2015; Narashimhan B.; Mallapragada S.K.; Peppas, 1999).

$$Q = Q_0 + K_0\, x\, t \qquad (5)$$

where Q_0 is the initial concentration of the active ingredient that is released at time zero (generally, $Q_0 = 0$), and K_0 is the zero-order constant.

The second model was the first-order model. This relationship could be used to describe drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices. The data were obtained by plotting the log cumulative released amount of drug (log (Q)) vs. time using Eq. 6 (Dash et al., 2010; Narashimhan B.; Mallapragada S.K.; Peppas, 1999).

$$LogQ = LogQ_0 + \frac{K}{2.303} x\, t \qquad (6)$$

where Q_0 is the initial concentration of the active ingredient released at time zero (generally, $Q_0 = 0$) and K is the first-order constant.

The third model was the Higuchi model (Bruschi, 2015a). Higuchi's model was applied to describe the diffusion pattern of a saturated drug in a liquid form compared to the release of a drug contained in a porous matrix. This model proposed that the matrix was nonswellable, and the diffusivity from this matrix was constant. The correlation coefficient was calculated for the cumulative released amount (Q) against the square route of time (t) (Eq. 7)

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

$$Q = K_H\sqrt{t} \quad (7)$$

where K_H is the release constant of Higuchi.

The fourth model was the Ritger–Peppas and Korsmeyer–Peppas model. This model describes the release of a drug molecule from a polymeric matrix, such as a hydrogel. The correlation coefficient and the value of the exponent (n) were calculated for ln (percentage of cumulative released amount ($\frac{M_i}{M_\infty}$) against ln (time (t) (Koros, W.; Punsalan, 2001) (Eq. 8).

$$\frac{M_i}{M_\infty} = Kt^n \quad (8)$$

where M_∞ is the total amount of drug contained in the dosage form, M_i is the amount of released drug at time t, n is the exponent of release, which can reflect the drug release mechanism of the drug, and K is a constant of geometrical and structural properties of the dosage form also it considered as the release velocity constant (Bruschi, 2015). The measurements were repeated three times to estimate the means and standard deviations.

Statistical analysis

Statistical analysis was performed using Minitab statistical software (v. 18 statistical pack, USA). The level of significance was $p<0.05$.

RESULTS

HPLC method and calibration curve

A calibration curve for IB was established for concentrations ranging between 0.05-0.8 mg•mL^{-1}. The calibration curve showed a correlation coefficient (r^2) of 0.999 and a

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

regression standard deviation of 4.03% (Figure 1A). The ratio of the height of the peak of the lowest concentration (0.05 mg•mL^{-1}) to the height of the peak of the noise was much higher than 9 times, indicating that the detection limit was much lower than 0.05 mg•mL^{-1} (Council of Europe, 2003; ICH, 2005).

Fig. 1. HPLC-(A): calibration curve, (B): Chromatograms of released ibuprofen from the tablets (1) after 1 h, (2) after 2 h, (3) after 3 h, (4) after 4 h, (5) after 5 h, after (6) 6 h and (7) after 20 h.

Flowability of granules

Using bulk density and tapped density, Carr's and Hausner indices were estimated and tabulated in Table 2 according to Eq. 2 and Eq. 3, respectively. The measured flowability of the physical mixture of IB and bentonite in Table 2 (Carr's index and corresponding Hausner ratio were 29.17 ± 1.1 and 1.41 ± 0.047, respectively) revealed a poor flowability for this mixture. On the other hand, Table 2 shows that Carr's indices and the corresponding Hausner ratios for different prepared granules were less than 16% and 1.2, respectively. Hence, the flowability was improved after granulation (USP-35, 2011). Despite a statistically significant difference in Carr's and Hausner indices among the different formulations (one-way ANOVA, $p < 0.001$ for both), flowability was appropriate for all formulations.

Table 2. The calculated flowability results using Carr's index and the Hausner ratio for all the prepared formulations (mean ±SD, n=3)

Formulation	Carr's Index (%)	Hausner Ratio
IB-bentonite not granulated	29.17 ± 1.1	1.41 ± 0.047
IB-MCC5	14.13 ± 0.55	1.15 ± 0.460
IB-MCC10	15.59 ± 0.43	1.18 ± 0.032
IB-W	20.42 ± 0.67	1.26 ± 0.041
IB-PEG5	15.75 ± 0.51	1.19 ± 0.038
IB-PEG10	14.41 ± 0.33	1.17 ± 0.027
IB-MCC10 dry	9.98 ± 0.21	1.11 ± 0.023

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

IB-starch10	8.20 ± 0.19	1.18 ± 0.027

FTIR spectra evaluation

The FTIR spectra of different pure components, granules and hydrated IB tablets are presented in Figure 2.

Fig. 2. FTIR spectra of pure IB, bentonite, water, granules of IB, and hydrated granules of IB without binder.

A broad band at wavenumbers between 3000–3700 cm^{-1} and a band that appeared at 1638 cm^{-1} were detected in the FTIR spectrum of water and were related to O–H stretching and bending vibrations, respectively. The FTIR spectrum of bentonite powder showed a sharp band at 1028 cm^{-1}, which was likely related to the stretching vibrations of Si-O in the Si-O-Si groups of the tetrahedral sheet. Additionally, the bands at 480 and 521 cm^{-1} were produced by Si-O-Al (octahedral sheet) and Si-O-Si bending vibrations. Moreover, the stretching O–H water band at 3000–3700 cm^{-1} was observed in the dried granules, indicating the presence of some moisture in the granules after drying. Furthermore, the intensity of this band and H_2O bending vibration at 1638 cm^{-1} increased in the hydrated bentonite tablets, whereas the intensity of the band of the stretch vibrations of Si-O in the Si-O-Si groups at 1028 cm^{-1} were reduced after the addition of water, indicating the presence of water between bentonite sheets (Senturk et al., 2009; Tabak, 2009; Youssef et al., 2014). The FTIR spectrum of IB presented in Figure 2 also showed characteristic bands at 2946, 1734, 1251, and 780 cm^{-1} for CH3 stretching, C=O stretching, =C-H in-plane deformation and CH_2 rocking, respectively (Mallick et al., 2008; Ramukutty & Ramachandran, 2012). However, the FTIR spectrum of IB in the dry and hydrated granules (Figure 2) showed all the characteristic bands related to ibuprofen without any shift of their

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

positions. A reduction in the intensity of the peaks could be attributed to the dilution effect of IB in the IB: bentonite granules. Based on the above results, it was concluded that there was no evidence of any chemical interaction between the IB and bentonite. Therefore, ibuprofen was compatible with bentonite in the used formulations.

DSC measurements

DSC thermograms were performed to identify any possible interactions between IB and bentonite in their physical mixtures. The measured thermograms are represented in Figure 3. The thermograms showed endothermic peaks at temperatures between 75-89 °C for IB, which complied with the published works in the literature (Tudja et al., 2001; Wahab et al., 2011). Furthermore, there were no significant changes in the peaks of the thermograms of pure IB in comparison with the peaks of the drug mixture with bentonite. Hence, there was no potential interaction between bentonite and IB.

Fig. 3. DSC thermograms of bentonite, pure ibuprofen, and a physical mixture of bentonite with ibuprofen.

Powder-XRD measurements

The obtained XRD patterns of pure bentonite and milled granules of IB in bentonite with a range of 2-100° are given in Figure 4. The XRD pattern of bentonite (Figure 4) showed that bentonite was composed of montmorillonite (Si_3.74 Al_2.O_3 Fe 0.03 Mg 0.02 • O_{11}) as a major component, cristobalite (SiO_2), albite (Na Al Si_3 O_8) as a feldspar mineral and microcline (K Al Si_3 O_8) as a feldspar mineral with different structures, rather than albite (Ikhtiyarova et al., 2012; Macías-Quiroga et al., 2018). In addition, Figure 4 shows that the XRD pattern of bentonite did not change its crystallinity after granulation with ibuprofen except for a slight shift in montmorillonite peaks to a lower degree. This may be related to

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

the increase in the lattice spacing of montmorillonite crystals due to intercalated drugs in the interlayer of montmorillonite (Pergher et al., 2017). Therefore, no significant change in the crystalline structure of bentonite due to the granulation process of IB with bentonite was observed. Using Bragg's equation (Eq. 4), the basal spacing (d001) was calculated for bentonite at 2 θ equal to 7.58° and 5.98° for bentonite-IB granules. The calculated basal spacing value for bentonite was 11.654 Å, while the granules had a basal spacing value of 14.768 Å. The basal spacing for bentonite, particularly montmorillonite, is in agreement with published results (Karaborni et al., 1996; Matusewicz et al., 2013). The slight increase in basal spacing upon granulation with IB could be attributed to the increase in lattice space, as discussed earlier. Additionally, Kalaleh et al. reported that the increase in basal spacing could be attributed to the formation of hydrogen bonds between IB and bentonite and water molecules that are retained from granulation (Kalaleh et al., 2013).

Fig. 4. XRD patterns of bentonite and bentonite-ibuprofen granules.

Quality control of tablets

The hardness and friability of the tablets were measured after tablet compression, and the mean values along with the standard deviations were calculated and are presented in Table 3.

Table 3. The hardness and friability results for the prepared ibuprofen-loaded tablets (mean ± SD)

Formulation	Hardness (N) (n=6)	Friability % (n=3)
IB-MCC5	246.6 ± 5.5	0.40 ± 0.01
IB-MCC10	250.3 ± 9.6	0.21 ± 0.02
IB-W	347 ± 8.5	0.29 ± 0.02
IB-PEG5	284.6 ± 7	0.46 ± 0.01

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

IB-PEG10	252.6 ± 10.2	0.39 ± 0.01
IB-starch10	195.2 ± 6	0.2 ± 0.02
IB-MCC10 dry	207.2 ± 16	0.39 ± 0.01

The results in Table 3 show that the friability decreased with increasing MCC and PEG concentrations from 5 to 10% w/w. In addition, binder-free tablets demonstrated higher hardness in comparison to the prepared tablets with binders. One-way ANOVA of the results of the hardness of various formulations showed that there was a significant difference among formulations ($p<0.001$). The results also revealed an association between the hardness and the friability results. However, the friability for all the prepared formulations was less than 0.5%, which is in accordance with the pharmacopeial requirements.

Release profile of coated and uncoated tablets

MCC, PEG-4000 with concentrations of 5 and 10% and starch with a concentration of 10% were used as binders for preparing 800 mg IB tablets. Formulations of IB and bentonite were prepared from granules made without any binder addition. The released amounts of IB in the dissolution vessel were estimated over 24 hrs using the corresponding HPLC method (Figure 1B). The dissolution profiles of different prepared tablets were established by plotting the percentage of the cumulative amount of IB released against time (Figures 5A and B).

To mimic the transit of formulated tablets through the gastrointestinal tract (GI), the uncoated tablets prepared by granulation were tested for dissolution in 0.1 N HCl at different time intervals. The immersed tablets did not withstand HCl. Hence, the tablets had to be protected from HCl by enteric coating. The two types of IB tablets, namely, IB-MCC5 and IB-w, that showed higher linearity of the release profile were selected to be

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

enteric-coated. The coated tablets were subjected to 0.1 N HCl for two hrs (USP-35, 2011). Two-milliliter samples were taken after two hours from the acidic media to test the amount of released IB and hence the resistance of the enteric coating to the acidic media. Then, the acidic media was replaced by 7.2 pH phosphate buffer, and the sampling was continued for 24 hrs. Overall, IB was not detected after two hours in the dissolution medium (acidic medium); therefore, the enteric coating of the formulated tablets maintained its integrity and did not disintegrate in the acidic media. The results are presented in Figure 5C.

Fig. 5. Dissolution profiles of the prepared IB tablets (A) by wet granulation: free binder (IB-W), 5% MCC (IB-MCC5), 10% MCC (IB-MCC10) and dry granulation 10% MCC (IB-MCC10 dry); (B) by wet granulation using 5% PEG (IB-PEG5), 10% PEG (IB-PEG10) and 10% starch (IB-starch10); and (C) of enteric coated (IB-MCC5) and enteric coated (IB-W). Mean (3) ± SD.

The next stage focused on modeling the release profiles. The correlation coefficients (r2) for released IB from the prepared tablets were estimated for each of the zero-order, first-order, Higuchi, and the Korsmeyer-Peppas models and are presented in Table 4.

The release modeling results indicated that the highest correlation coefficients were observed for Korsemeyer-Peppas, followed by the zero-order model and then the Higuchi model, while the lowest determined coefficients were for the first-order model. However, the estimated n values of the Korsmeyer-Peppas model for IB-PEG5, IB-MCC5 and IB-starch10 were close to 1. On the other hand, the IB-W (without binder), enteric-coated, IB-PEG10 and IB-MCC10 (Binder concentration of 10%) showed (n) values between 1.12 and 1.35. Furthermore, K which is the release rat constant was calculated from the intercept of Ritger–Peppas and Korsmeyer–Peppas's equation (Eq. 8). The results in Table 4 showed that the rat constants were low from enteric coated tablets and form free binder tablets (IB-W). On other hand, it was the highest from prepared tablets using MCC by dry granulation.

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

Which means that the release was slower from the enteric coated tablets and from free binder tablets (IB-W) in comparison to other formulated tablets. Furthermore, the estimated intercept values of the zero order equation model were negative in case of enteric coated tablets and free binder tablets, whereas was the highest in case of prepared tablets using MCC by dry granulation which comes along with previous mentioned results of release rate constant that the intercept of zero order equation model refers to the initial released amount.

Table 4. The correlation coefficients of percentage of cumulative released amount against time for the Higuchi model, logarithm of percentage of cumulative released amount against time (first order), zero-order model, and Ritger–Peppas and Korsmeyer–Peppas model.

Formulation	Higuchi model		First-order model		Zero-order model		Korsemeyer Peppas model		
	r^2	Intercept	r^2	Intercept	r^2	Intercept	r^2	k	n
IB-W	0.935	- 23.19	0.844	0.52	0.996	- 2.70	0.986	2.47	1.26
IB-PEG5	0.892	- 17.03	0.763	1.05	0.821	10.38	0.936	5.85	1.03
IB-PEG10	0.978	- 29.76	0.773	1.05	0.917	6.50	0.961	5.47	1.15
IB- MCC5	0.990	- 23.35	0.826	3.88	0.977	0.92	0.974	4.22	0.95
IB-MCC10	0.982	-25.20	0.766	4.10	0.985	1.10	0.967	4.48	1.12
IB-MCC10dry	0.944	- 12.21	0.759	1.36	0.823	21.71	0.986	12.09	0.91
IB-starch10	0.985	- 24.52	0.826	1.21	0.995	11.77	0.974	9.07	0.94
Coated IB-MCC5	0.956	- 35.95	0.726	0.67	0.994	- 7.18	0.954	1.94	1.30
Coated IB-W	0.985	- 41.71	0.788	0.56	0.975	- 9.83	0.98	1.61	1.35

DISCUSSION

In many previous studies, bentonite was not solely used to produce a sustained-release formulation of the incorporated drugs. Oliveira *et al.* (2017) investigated the incorporation of olanzapine into montmorillonite dispersed in a mixture of alginate and xanthan gum biopolymers to achieve a controlled-release profile (Pergher et al., 2017). Additionally, García-Guzmán *et al.* (2018) used a blend of gelatin carrier and montmorillonite to evaluate

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

its capability as a controlled drug delivery system for atorvastatin (García-Guzmán et al., 2018). In addition, Joshi *et al.* (2010) prepared sustained-release ranitidine tablets using montmorillonite as a carrier by an ion exchange approach (Joshi et al., 2010). Dziadkowiec & coworkers (2017) reported that the prepared ibuprofen-salt loaded nanocomposite from bentonite and neutral guar gum released ibuprofen in a controlled manner (Dziadkowiec et al., 2017). Similarly, Alkrad *et al.* (2017) used a 50% mixture of bentonite with different drugs to study the release behavior from prepared tablets by direct compression (Alkrad et al., 2017). The produced blends had poor flowability, which was considered the main limitation of the direct compression method (Aulton & Taylor, 2013; Franc et al., 2018; Timmins et al., 1991). Hence, the current investigation was designed to granulate bentonite before compression to improve flowability and enable large-scale production of IB-bentonite tablets.

The FTIR spectroscopy, thermal analysis using DSC and powder XRD analysis did not reveal any changes to IB after mixing with bentonite. Both IB and bentonite retained their characteristic features upon formulation. Consequently, bentonite was a compatible ingredient with the granulated drug in this study. However, by employing wet granulation, the reported poor flowability of bentonite was improved in the current investigation, thus eliminating the main hindrance for preparing sustained release tablets using bentonite (Gao et al., 1995). The solid bridges were the main force that remained between the particles in the dry granules. This was attributed to the hardening process of the binder or recrystallization of the dissolved materials upon drying the wet granules (Aulton & Taylor, 2013; Olsson & Nyström, 2001). However, the granules of IB and bentonite could be formulated using water alone without any additional binder. The binding force between

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

these particles in dry granules was likely to be attributed to solid bridges formed by the recrystallization of the dissolved materials in water.

The produced granules had good flowability, as the granules had higher weight and less specific surface area than separate particles. Furthermore, the hardness of the compressed granules was high and provided the tablets with enough mechanical strength to prevent rapid disintegration upon contact with the buffer (Saravanan et al., 2002). The mechanical strength between different tablets with or without a binder was comparable. It was even higher in the case of IB tablets without any binder. The key binding forces within the formulated tablets could be attributed to the interactions between bentonite-bentonite particles. Several studies have reported the good compactability of bentonite (Gattermann et al., 2001; Gökalp et al., 2011). Moreover, the compacted commercial granulated clay mineral (magnesium aluminum smectite, gMgSm) showed good cohesive strengths and higher porosity after compression than MCC; hence, it could be used to formulate tablets (Laity et al., 2015).

Furthermore, the results of the release studies revealed that the employed binders did not influence or slow the release through the gel matrix of the tablets prepared by the wet or dry granulation process in comparison to tablets prepared without any binder. Statistical analysis of the release profile of the formulations showed that there was no significant difference between the formulations in the release pattern (one-way ANOVA, $p=0.9277$). In addition, the results in Table 3 and Table 4 show that the increase in the hardness was not reflected by slowing the release of IB.

Visual observation of the tablets during the dissolution test (Figure 6) showed that bentonite forms a gel structure in dissolution media at pH 7.2, whereas the tablets

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

disintegrated at lower acidic pH, which could be related to the dissolution of montmorillonite at low pH, which was responsible for gel-building in bentonite (Alkrad et al., 2017; Bendou & Amrani, 2014; González-Santamaría et al., 2020; Mouzon et al., 2016).

Fig. 6. Photographs of IB-bentonite tablets (A) & (B) tablets before dissolution study, (C) the tablet at zero time in dissolution apparatus, the photographs (D-G) represent gel structure of IB-bentonite tablets upon dissolution in a dissolution medium using phosphate buffer pH 7.2 after (D): 1 hr; (E): 2 hrs; (F): 3 hrs; (G): 24 hrs.

To protect IB-bentonite tablets from harsh acidic media, enteric coating was carried out. The results of this work revealed that enteric-coated tablets resisted 0.1 N HCl for two hrs. This coating was vital to protect bentonite from hydrolysis upon exposure to the acidic media in the stomach.

The next step focused on assessing the release kinetics of the formulated tablets. Table 4 shows high correlation coefficients in the case of zero-order fitting, which were between 0.95 and 0.99 for the different formulated tablets (except the tablets prepared with PEG and IB-MCC10 dry). The results also indicated that IB was released from the bentonite gel-forming matrix in a sustained manner. Furthermore, the release data were fitted using the Korsmeyer–Peppas model to determine the mechanism of drug release from the bentonite gel-forming matrix. The Korsmeyer–Peppas model assesses the release of drugs from a swelling gel structure ("Mathematical Models of Drug Release," 2015). The results showed a high correlation coefficient with this model.

The Korsmeyer–Peppas model differentiated between Fickian and non-Fickian models according to the "n" value. When n = 0.5, the model is Fickian (Case I), and the drug is released by diffusion and is characterized by high solvent diffusion inside the matrix and

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

low polymeric relaxation. When n> 0.5, the model is non-Fickian, which is associated with vitreous polymers and can be classified into three subtypes. The first subtype of the non-Fickian model is anomalous release when $0.5 < n < 1$. Generally, the diffusion and relaxation rates by this model are comparable. The second subtype of the non-Fickian mode (Case II) is when $n = 1$. In this model, the velocity of solvent diffusion is less than that of the polymeric relaxation process. The drug release rate is constant, and the order of release is zero. Finally, the third subtype of the non-Fickian model is the super Case II model when $n > 1$. In the super case II model, the velocity of solvent diffusion is much higher, causing an acceleration of solvent penetration (Klech & Simonelli, 1989). In this study, the values n of IB-PEG5, IB-MCC5, and IB-starch10 were close to 1, indicating that the drug was released according to the non-Fickian zero order. On the other hand, the prepared tablets without binder, enteric-coated tablets and when the concentrations of the binder in IB-PEG5 and IB-MCC5 were increased from 5 to 10%, the n value was higher than 1.12 and less than 1.35. Such results indicated that the release from these tablets was according to case II (zero order) and super case II. The results suggested that there was an increase in solvent diffusion in such cases through the swelled tablets. However, the results revealed that an "n" value closer to 1, such as IB-PEG5 and IB-PEG10, was not always associated with an increase in the correlation coefficient value in the case of zero-order correlation.

Overall, varying the binder concentration could lead to a targeted release pattern. The produced formulations using a cost-effective excipient such as bentonite to formulate tablets containing a high dose of IB, a challenging active ingredient, were accomplished using a commonly used binder or even without a binder.

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

CONCLUSION

In this research, bentonite was investigated for the development of sustained release tablets containing a high dosing/load drug such as ibuprofen. Wet and dry granulation techniques were employed to prepare IB-bentonite tablets. Molecular and thermal profiling confirmed the compatibility of IB with bentonite. Furthermore, the granulation process improved the poor flowability of bentonite, which is advantageous for large-scale manufacturing purposes. In addition, this work showed that bentonite acts as a binding agent and has good compaction characteristics, which produced tablets with high mechanical strength. Upon dissolution, bentonite tablets formed a gel matrix that enabled sustained release of IB over 24 hrs. In addition, the enteric coating of the optimal formulations protected the gel structure of bentonite from degradation in the acidic media. The release kinetics of IB from the optimal formulation followed case II (zero order) and super case II, suggesting an increase in solvent diffusion through the swelled tablets. Based on these findings, bentonite could be a potential excipient for formulating sustained-release tables containing high-dosing drugs.

Acknowledgment

The authors would like to express their appreciation for Isra University for funding this project and the United Pharmaceuticals Company Limited for the generous donation of ibuprofen and enteric coating materials, as well as for the permission to use the coater system in the research and development department.

Ethics approval

Not applicable

Funding

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

The research was funded by Isra University.

Data availability

All raw data are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Authors' contributions

Jamal Alkrad: Conceptualization, methodology, investigation, and original draft preparation. **Sind Al-Sammarraie**: Data curation, investigation. **Eman Dahmash**: Writing- reviewing and editing and statistical analysis. **Nidal Qinna:** Critical reviewing and editing the original draft. **Abdallah Y Naser:** Statistical evaluation.

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

REFERENCES

Agarwal, G., Agarwal, S., Karar, P., & Goyal, S. (2017). Oral Sustained Release Tablets: An Overview with a special emphasis on Matrix Tablet. *American Journal of Advanced Drug Delivery*, *5*(2), 64–77.

Alkrad, J. A., Abu Shmeis, R., Alshwabkeh, I., Abazid, H., & Mohammad, M. A. (2017). Investigation of the potential application of sodium bentonite as an excipient in formulation of sustained release tablets. *Asian Journal of Pharmaceutical Sciences*, *12*(3), 259–265. https://doi.org/10.1016/j.ajps.2017.01.004

Aulton, M. E., & Taylor, K. (2013). *Aulton's pharmaceutics: the design and manufacture of medicines*. Elsevier Health Sciences.

Bechgaard, H., & Nielsen, G. H. (1978). Controlled-release multiple-units and single-unit doses a literature review. *Drug Development and Industrial Pharmacy*, *4*(1), 53–67.

Bendou, S., & Amrani, M. (2014). Effect of hydrochloric acid on the structural of sodic-bentonite clay. *Journal of Minerals and Materials Characterization and Engineering*, *2014*.

Boek, E. S., Coveney, P. V, & Skipper, N. T. (1995). Monte Carlo molecular modeling studies of hydrated Li-, Na-, and K-smectites: Understanding the role of potassium as a clay swelling inhibitor. *Journal of the American Chemical Society*, *117*(50), 12608–12617.

Bruschi, M. L. (2015). *Strategies to modify the drug release from pharmaceutical systems*. Woodhead Publishing.

Cao, Q.-R., Choi, J.-S., Liu, Y., Xu, W.-J., Yang, M., Lee, B.-J., & Cui, J.-H. (2013). A formulation approach for development of HPMC-based sustained release tablets for tolterodine tartrate with a low release variation. *Drug Development and Industrial Pharmacy*, *39*(11), 1720–1730.

Chakraborty, S., Pandit, J. K., & Srinatha, A. (2009). Development of extended release divalproex sodium tablets containing hypdrophobic and hydrophilic matrix. *Current Drug Delivery*, *6*(3), 291–296.

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

Chaw, C. S., Yazaki, E., & Evans, D. F. (2001). The effect of pH change on the gastric emptying of liquids measured by electrical impedance tomography and pH-sensitive radiotelemetry capsule. *International Journal of Pharmaceutics*, *227*(1–2), 167–175.

Chen, X., Wen, H., & Park, K. (2010). Challenges and new technologies of oral controlled release. *Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice*, *16*, 257–277.

Council of Europe. (2003). *European Pharmacopoeia: Monograph chromatographic separation techniques* (Council of Europe (Ed.); 4th ed.). European Directorate for the Quality of Medicine & Health Care of the Council of Europe (EDQM),.

Dash, S., Murthy, P. N., Nath, L., & Chowdhury, P. (2010). Kinetic modeling on drug release from controlled drug delivery systems. *Acta Pol Pharm*, *67*(3), 217–223.

Dziadkowiec, J., Mansa, R., Quintela, A., Rocha, F., & Detellier, C. (2017). Preparation, characterization and application in controlled release of Ibuprofen-loaded Guar Gum/Montmorillonite Bionanocomposites. *Applied Clay Science*, *135*, 52–63.

FDA. (2021). *Code of Federal Regulations Title 21- Sec. 184.1155 Bentonite*.

Franc, A., Vetch\`y, D., Vodáčková, P., Kubal'ák, R., Jendryková, L., & Goněc, R. (2018). Co-processed excipients for direct compression of tablets Společně zpracované pomocné látky pro p{\v{r}}{\'\i}mé lisován{\'\i} tablet. *Češ. Slov. Farm*, *67*, 175–181.

Gao, P., Nixon, P. R., & Skoug, J. W. (1995). Diffusion in HPMC gels. II. Prediction of drug release rates from hydrophilic matrix extended-release dosage forms. *Pharmaceutical Research*, *12*(7), 965–971.

García-Guzmán, P., Medina-Torres, L., Calderas, F., Bernad-Bernad, M. J., Gracia-Mora, J., Mena, B., & Manero, O. (2018). Characterization of hybrid microparticles/Montmorillonite composite with raspberry-like morphology for Atorvastatin controlled release. *Colloids and Surfaces B: Biointerfaces*, *167*, 397–406.

Gattermann, J., Wittke, W., & Erichsen, C. (2001). Modelling water uptake in highly

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

compacted bentonite in environmental sealing barriers. *Clay Minerals*, *36*(3), 435–446.

Ghosal, K., Chakrabarty, S., & Nanda, A. (2011). Hydroxypropyl methylcellulose in drug delivery. *Der Pharmacia Sinica*, *2*(2), 152–168.

Gökalp, Z. ., Ba\csaran, M., & Uzun, O. (2011). Compaction and swelling characteristics of sand-bentonite and pumice-bentonite mixtures. *Clay Minerals*, *46*(3), 449–459.

González-Santamaría, D. E., Fernández, R., Ruiz, A. I., Ortega, A., & Cuevas, J. (2020). High-pH/low pH ordinary Portland cement mortars impacts on compacted bentonite surfaces: Application to clay barriers performance. *Applied Clay Science*, *193*, 105672.

Haoue, S., Derdar, H., Belbachir, M., & Harrane, A. (2020). Polymerization of ethylene glycol dimethacrylate (EGDM), using an Algerian clay as eco-catalyst (maghnite-H+ and Maghnite-Na+). *Bulletin of Chemical Reaction Engineering & Catalysis*, *15*(1), 221–230.

Hun Kim, M., Choi, G., Elzatahry, A., Vinu, A., Bin Choy, Y., & Choy, J.-H. (2016). Review of clay-drug hybrid materials for biomedical applications: Administration routes. *Clays and Clay Minerals*, *64*(2), 115–130.

ICH. (2005). Validation of analytical procedures: Text and methodology Q2(R1). *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*, *4*.

Ikhtiyarova, G. A., Özcan, A. S., Gök, Ö., & Özcan, A. (2012). Characterization of natural-and organobentonite by XRD, SEM, FT-IR and thermal analysis techniques and its adsorption behaviour in aqueous solutions. *Clay Minerals*, *47*(1), 31–44.

Joshi, G. V, Kevadiya, B. D., & Bajaj, H. C. (2010). Controlled release formulation of ranitidine-containing montmorillonite and Eudragit® E-100. *Drug Development and Industrial Pharmacy*, *36*(9), 1046–1053.

Kalaleh, H.-A., Tally, M., & Atassi, Y. (2013). Preparation of a clay based superabsorbent polymer composite of copolymer poly (acrylate-co-acrylamide) with

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

bentonite via microwave radiation. *ArXiv Preprint ArXiv:1311.6445*.

Karaborni, S., Smit, B., Heidug, W., Urai, J., & Van Oort, E. (1996). The swelling of clays: molecular simulations of the hydration of montmorillonite. *Science*, *271*(5252), 1102–1104.

Klech, C. M., & Simonelli, A. P. (1989). Examination of the moving boundaries associated with non-fickian water swelling of glassy gelatin beads: Effect of solution pH. *Journal of Membrane Science*, *43*(1), 87–101.

Laity, P. R., Asare-Addo, K., Sweeney, F., Šupuk, E., & Conway, B. R. (2015). Using small-angle X-ray scattering to investigate the compaction behaviour of a granulated clay. *Applied Clay Science*, *108*, 149–164.

Li, C., Wang, M., Liu, Z., Xu, Y., Zhou, C., & Wang, L. (2021). Kaolinite-armoured polyurea microcapsules fabricated on Pickering emulsion: controllable encapsulation and release performance of a lipophilic compound. *Clay Minerals*, *56*(1), 46–54.

Macías-Quiroga, I. F., Giraldo-Gómez, G. I., & Sanabria-González, N. R. (2018). Characterization of colombian clay and its potential use as adsorbent. *The Scientific World Journal*, *2018*.

Mallick, S., Pattnaik, S., Swain, K., De, P. K., Saha, A., Mazumdar, P., & Ghoshal, G. (2008). Physicochemical characterization of interaction of ibuprofen by solid-state milling with aluminum hydroxide. *Drug Development and Industrial Pharmacy*, *34*(7), 726–734.

Mathematical models of drug release. (2015). In *Strategies to Modify the Drug Release from Pharmaceutical Systems*. https://doi.org/10.1016/b978-0-08-100092-2.00005-9

Matusewicz, M., Pirkkalainen, K., Liljeström, V., Suuronen, J.-P., Root, A., Muurinen, A., Serimaa, R., Olin, M., & Adams, J. (2013). Microstructural investigation of calcium montmorillonite. *Clay Minerals*, *48*(2), 267–276.

Mouzon, J., Bhuiyan, I. U., & Hedlund, J. (2016). The structure of montmorillonite gels revealed by sequential cryo-XHR-SEM imaging. *Journal of Colloid and Interface*

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

Science, *465*, 58–66.

Narashimhan B.; Mallapragada S.K.; Peppas, N. A. (1999). Release kinetics, data interpretation. In E. Mathiowitz (Ed.), *Encyclopedia of controlled drug delivery* (1st editio). Wiley-interscience.

Nutting, P. G. (1943). *The action of some aqueous solutions on clays of the montmorillonite group*. US Government Printing Office.

Olsson, H., & Nyström, C. (2001). Assessing tablet bond types from structural features that affect tablet tensile strength. *Pharmaceutical Research*, *18*(2), 203–210.

Pergher, S. B. C., Oliveira, A. S., & Alcântara, A. (2017). Bionanocomposite systems based on montmorillonite and biopolymers for the controlled release of olanzapine. *Mater Sci Eng C Mater Biol Appl*, *75*(1), 1250–1258.

Ramukutty, S., & Ramachandran, E. (2012). Growth, spectral and thermal studies of ibuprofen crystals. *Crystal Research and Technology*, *47*(1), 31–38.

Saravanan, M., Nataraj, K. S., & Ganesh, K. S. (2002). The effect of tablet formulation and hardness on in vitro release of cephalexin from Eudragit L100 based extended release tablets. *Biological and Pharmaceutical Bulletin*, *25*(4), 541–545.

Senturk, H. B., Ozdes, D., Gundogdu, A., Duran, C., & Soylak, M. (2009). Removal of phenol from aqueous solutions by adsorption onto organomodified Tirebolu bentonite: Equilibrium, kinetic and thermodynamic study. *Journal of Hazardous Materials*, *172*(1), 353–362.

Sharma, A. K., Mortensen, A., Schmidt, B., Frandsen, H., Hadrup, N., Larsen, E. H., & Binderup, M.-L. (2014). In-vivo study of genotoxic and inflammatory effects of the organo-modified Montmorillonite Cloisite® 30B. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*, *770*, 66–71.

Tabak, A. (2009). Structural analysis of reactive dye species retained by the basic alumina surface. *Journal of Thermal Analysis and Calorimetry*, *95*(1), 31–36.

Tantishaiyakul, V. (2004). Prediction of aqueous solubility of organic salts of diclofenac

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

using PLS and molecular modeling. *International Journal of Pharmaceutics*, *275*(1–2), 133–139.

Timmins, P., Delargy, A. M., Howard, J. R., & Rowlands, E. A. (1991). Evaluation of the granulation of a hydrophilic matrix sustained release tablet. *Drug Development and Industrial Pharmacy*, *17*(4), 531–550.

Tudja, P., Khan, M. Z. I., MEŠTROVIC, E., HORVAT, M., & GOLJA, P. (2001). Thermal behaviour of diclofenac sodium: decomposition and melting characteristics. *Chemical and Pharmaceutical Bulletin*, *49*(10), 1245–1250.

USP-35. (2011). *The United States pharmacopeia : the National Formulary : USP 35 NF 30th Edition* (I. Authority of the United States Pharmacopeial Convention (Ed.)). USP, C. (2011). The United States Pharmacopeia. National Formulary.

Van Olphen, H. (1953). Interlayer forces in bentonite. *Clays and Clay Minerals*, *2*(1), 418–438.

Wahab, A., Khan, G. M., Akhlaq, M., Khan, N. R., Hussain, A., Zeb, A., & Shah, K. U. (2011). Pre-formulation investigation and in vitro evaluation of directly compressed ibuprofen-ethocel oral controlled release matrix tablets: A kinetic approach. *African Journal of Pharmacy and Pharmacology*, *5*(19), 2118–2127.

Wen, H., & Park, K. (2011). *Oral controlled release formulation design and drug delivery: theory to practice*. John Wiley & Sons.

Willhite, C. C., Ball, G. L., & McLellan, C. J. (2012). Total allowable concentrations of monomeric inorganic aluminum and hydrated aluminum silicates in drinking water. *Critical Reviews in Toxicology*, *42*(5), 358–442.

Youssef, A. M., Al-Awadhi, M. M., & Akl, M. A. (2014). Solid phase extraction and spectrophotometric determination of methylene blue in environmental samples using bentonite and acid activated bentonite from Egypt. *Journal of Analytical & Bioanalytical Techniques*, *5*(1), 1–8.

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

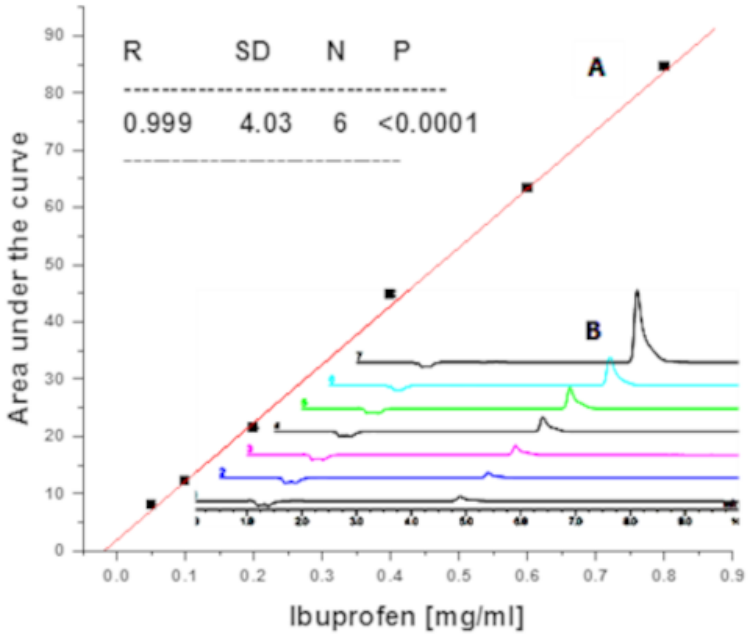

Figure 1

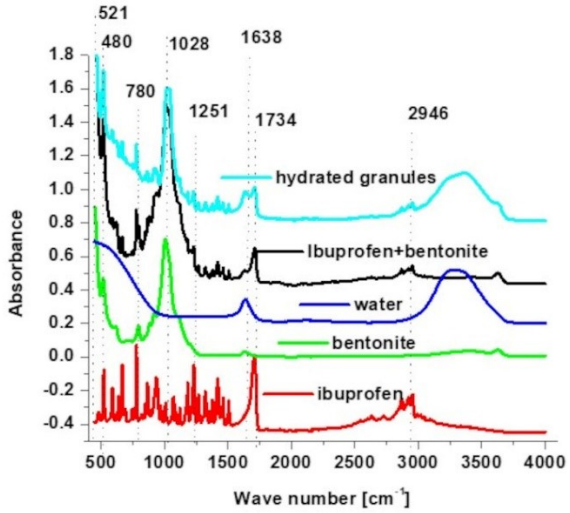

Figure 2

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

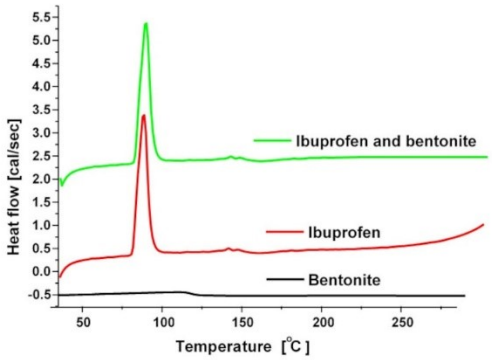

Figure 3

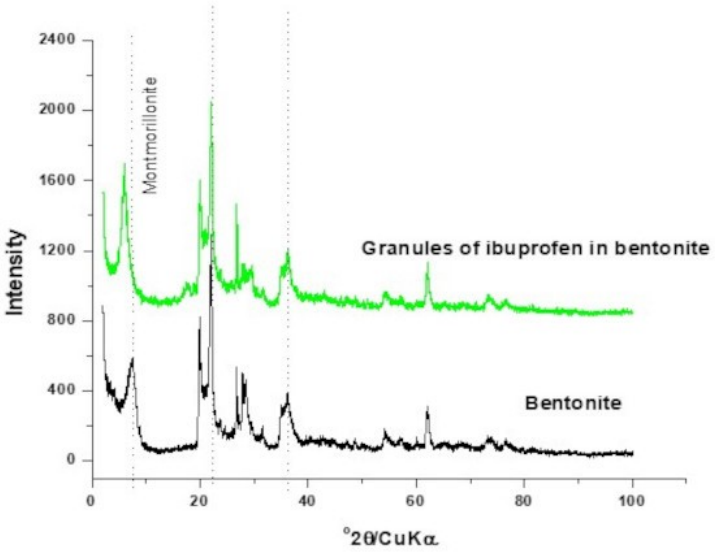

Figure 4

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

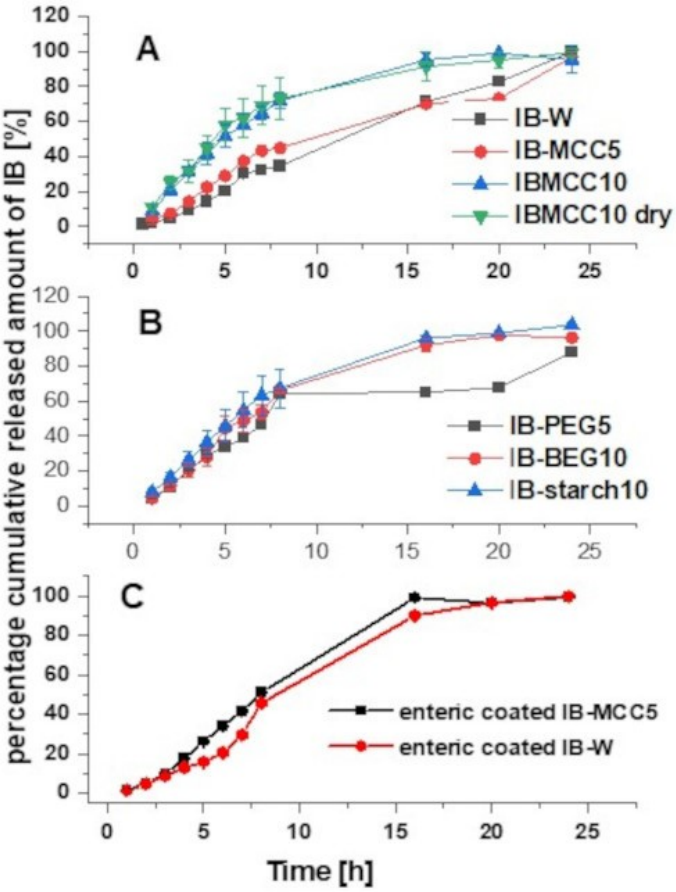

Figure 5

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press

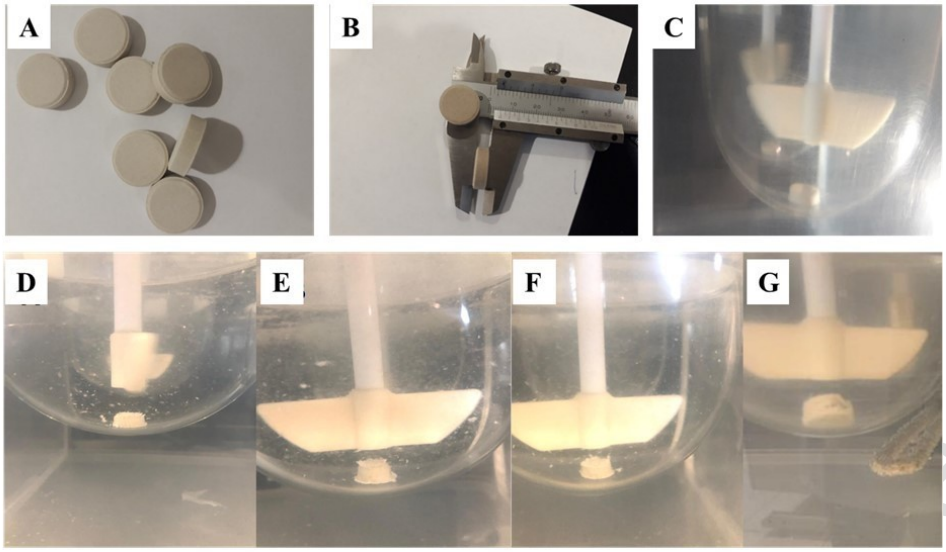

Figure 6

https://doi.org/10.1180/clm.2022.35 Published online by Cambridge University Press