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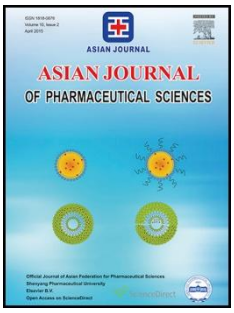


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Author: Jamal Alyoussef Alkrad, Reham Abu Shmeis, Iyad Alshwabkeh, Husam Abazid, Mohammad Amin Mohammad

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

**Jamal Alyoussef Alkrad[1,*], Reham Abu Shmeis[1], Iyad Alshwabkeh[1], Husam Abazid[1] Mohammad Amin Mohammad[1,2]**

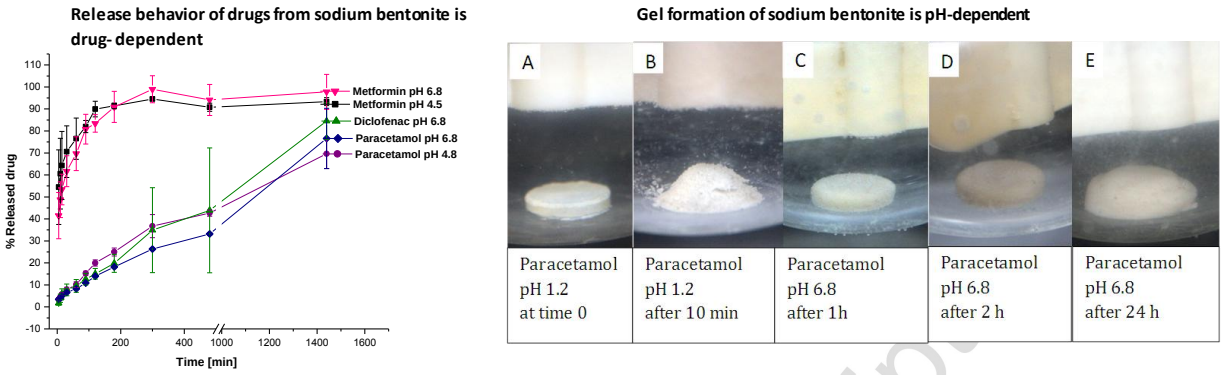
[1] Faculty of Pharmacy, Isra University, PO Box 22 and 23, Amman, Jordan.

[2] School of Pharmacy, University of Bradford, Bradford, BD7 1DP, UK.

*Corresponding author:

Jamal Alyoussef Alkrad, Tel: 00962789696157, E-mail: jamal.alkrad@iu.edu.jo

Graphical Abstract




**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.

**Keywords:**

Direct compression; sustained release; excipients; sodium bentonite.

## 1. Introduction:

European pharmacopeia (2003) defined bentonite as a naturally occurring mineral clay consisting mainly of montmorillonite which is a hydrated aluminium 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 is 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 a 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 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 flourouracil to produce a composite of 5 florouracil/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:

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

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

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.

$$\%Friability = [(W_I - W_F)/W_I] \times 100 \qquad (3)$$

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 Elmer UATR Two, Li600301 spectrum made in liantrisant, UK) for each of paracetamol, diclofenac sodium, metformin HCl, SB powders and their mixtures with SB. The measured FTIR-spectra of pure drug and drugs SB mixture were measured between 450 and 3950 ($cm^{-1}$).

2.2.7 Dissolution test performance and sampling:

Dissolution testing was performed using USP II dissolution tester (Hanson Research SR6) over 24 hours at rotation speed of 50 rpm and 37ºC. The used volume of the dissolution test was 900 ml of either HCl, acetate and phosphate buffers at pH 1.2, 4.5 and 6.8 respectively (USP 34). A 2.5 ml samples were withdrawn according to the following time interval 10, 15, 30, 45, 90, 120, 180, 300, 480 and 1440 min. Samples were filtered and assayed using HPLC according to the assay methods.

2.2.8 High pressure liquid chromatogram (HPLC) Assay:

Analysis was performed using chromatographic system of Thermo Scientific, Dionex Ultimate 3000 HPLC connected with diode array detector (Germany). The pharmacopeial HPLC methods were used.

HPLC method for Paracetamol was according to USP 34 where water and methanol (700:300) were used as a mobile phase at flow rate of 2 ml/min for a total run time of 3 min. A C18 column system was used (250x4.6 mm), supplied by Thermoscientific. The injection volume was 20 µL. The detection of the drug was carried out at 295 nm. A calibration curve was plotted for concentrations between 5.25 and 0.0015 mg/ml. The calibration curve showed correlation coefficient (r) of 0.9996 and the calibration line equation was y = 33.757x + 3.0166. HPLC method for assaying of diclofenac sodium was carried out using a mobile phase consisting of a water and methanol (300:700) using a flow rate of 1.5 ml/min with a total runtime of 6 mins. The column system was the same as the one mentioned previously and the injection volume for diclofenac sodium was 5 µL. A calibration curve was plotted for concentrations between 0.5 and 0.001 mg/ml to determine the content testing dissolution profile estimation. The calibration line equation was y = 89.008x + 0.0191 with correlation coefficient (r) of 0.9994.

Metformin HCl assay was carried out using C8, 5 µ (250 X 4.6 mm) column supplied by a thermo Quest (Hypersil Division). The mobile phase was a mixture of ion pair buffer: methanol:acetonitrile:tetrahydrofurane with ratio of 1000:1:1:2 v:v respectively. The ion pair buffer was prepared by dissolving 6g sodium chloride in 1 L bi-distilled water and adjusting this solution at pH 3 using diluted HCl then the buffer was filtered through a 0.45 µm membrane filter. The degassed mobile phase was run at a flow rate of 1ml/ min for time of 2.5 min. Metformin HCl was detected at wave length of 236 nm for injection volume of 20 µL. A series was prepared from a standard for concentrations between 0.3 and 0.001 for plotting the calibration curve. The equation of the calibration line was y = 1184.8x + 11.653 with correlation coefficient between the concentration and areas under peaks (r) of 0.999.

2.2.9 In vitro bioavailability and kinetics evaluation

The area under the curve (AUC) and mean dissolution time (MDT) were used as parameters for evaluating each of in vitro bioavailability and drugs kinetic. Both, the AUCs which were evaluated by trapezoidal method and the dissolution data which were fitted according to Hill model were estimated by Phoenix®WinNonlin® 6.4 program (Licensed by Pharasight):

Hill Model is fitted according to the following equation:

$$y(t) = (Finf * t^b) / (MDT^b + t^b) \qquad (4)$$

Where the estimated parameters are: Finf = amount released at time infinity, using the preferred units for y MDT = mean dissolution time, in the preferred units for x (time), b = slope factor.

2.2.10 Statistical evaluation

Each test was repeated three times then the means and standard deviations were calculated. The similarity of the results was tested by t-Test with confidence interval 95% ($P < 0.05$).

**3. Results and discussion:**

The flowability of the compressed powder is an important factor in direct compression [14]. The flowability results of different SB mixtures are represented in Table 1. The metformin hydrochloride: SB mixture had poor flowability. However, the paracetamol: SB mixture and diclofenac sodium: SB mixture resulted in very poor flowability according to the USP 34.

[Table 1]

The hardness of compressed tablets was adjusted at 145 ± 10 newton. Twenty tablets were weighed individually and no one tablet deviated by 5% from 1 g. Moreover, for each drug, the friability of produced tablets was less than 1% loss in the tablets' weight after the test, and so the tablets complied with the USP requirements for friability and mass uniformity tests.

The DSC thermograms were measured to detect any phase transformation induced by the possible interaction between drugs and SB. The thermograms are represented in Fig. 1.

[Figure 1]

Figure 1 shows that the melting point of active pharmaceutical ingredients did not change significantly in their mixtures with SB. This suggests that no significant interaction between the SB and the drugs can be detected by DSC.

Moreover, the FTIR-measurements were performed to support DSC findings. The FTIR-spectra are represented in Fig. 2.

[Figure 2]

The FTIR spectra are another evidence of the compatibility between the drugs and SB. FTIR spectra did not show any new peaks in the mixtures.

Three different drugs with different solubilities (paracetamol, diclofenac sodium and metformin HCl) were used for evaluating the dissolution behavior of direct compressed SB tablets in different physiologic pH values (pH 1.2, 4.5 and 6.8). The dissolution profiles of direct compressed tablets of the different drugs are represented in Fig. 3.

[Figure 3]

The dissolution profiles of direct compressed paracetamol tablets are represented in Fig. 3A. The paracetamol tablets released 37% and 85 % after 15 and 60 min, respectively, in pH 1.2 which is close to the requirements of paracetamol extended release tablets as mentioned in USP34 (45- 65 % and 60-85% at 15 and 60 mins respectively). Moreover, the released amount of paracetamol after 1.5 and 24 h were 10.2, 36.7 and 69.5%, respectively, in pH 4.5 and 8.2, 26.25 and 76.57 %, respectively, in pH 6.8. Therefore, the produced tables extended the paracetamol release in all three used pH values.

Figure 3B shows that the percent dissolved amount of diclofenac sodium after 1.5 and 24 h were 8.2, 34.8 and 84.5 % respectively in pH 6.8. These data propose a clear extended release for diclofenac sodium from its tablets over 24 h in pH 6.8.

Since, Diclofenac sodium is a weak acid drug and its pKa is 3.8, and so its solubility in aqueous dissolution medium decreases with lowering pH value, the released diclofenac was recrystallized in the dissolution medium at pH 1.2 and 4.5 make the medium turbid which hindered the following measurement [17].

Furthermore, the three different release profiles of metformin HCl in different pH (1.2, 4.5 and 6.8) are represented in Fig. 3C.

The percent dissolved amounts of metformin HCl were 54, 76.7 and 87.5% in pH 1.2, 60.5, 76.5 and 87.5 % in pH 4.5 and 48.7, 69.7 and 83.4 in pH 6.8 after 15, 60 and 120 min respectively. These dissolution profiles represent immediate release behavior in the different three pH media (USP 34).

The sustained release behavior of diclofenac sodium in pH 6.8 and paracetamol in pH 4.5 and 6.8 was observed after swelling the tablets in dissolution media [1]. To investigate the gel structure formation, FTIR-spectra were measured for bentonite as a powder as well as after forming gel and the results are represented in Fig. 4.

**[Figure 4]**

FTIR-spectrum of water showed a broad band was detected at 3000- 3700 $cm^{-1}$ which can be caused by the O–H stretching vibration and band is appeared at 1625 $cm^{-1}$ of $H_2O$ bending vibration. However FTIR-spectrum of bentonite powder showed a band at 3625 1/cm of the Si–

OH stretching band. A shifting in the broad band of water O–H stretching and a shoulder at 3650 $cm^{-1}$ were observed in wetted bentonite tablet which can be caused by Si–OH stretching band and HO–H vibration of the $H_2O$ adsorbed on silica surface [18].

The in vitro availability and kinetics of different drugs are estimated by calculation each area under the curve percent released amount against time curve (AUC) and mean dissolution time (MDT) from dissolution results. The calculated values using Pheonix® program are tabulated in Table 2:

[Table 2]

The results show short mean dissolution time in general (MDT) for the different drugs in medium of pH 1.2. However, the mean MDT was much longer in case of pH 4.5 and 6.8 for diclofenac and paracetamol in comparison to metformin HCl. Also, the in vitro availability was much higher for paracetamol in pH 1.2 comparing to pH 4.5 and 6.8, where metformin HCl showed similar availability in different pH values.

Sodium bentonite (SB) as excipient helped to produce immediate and sustained release tablets. Both paracetamol and Metformin HCl showed in simulated gastric juice pH 1.2 (Figs 3, 5) immediate release. Furthermore, the dissolution was faster in case of metformin HCl with MDT of 16.64 min comparing to paracetamol with MDT of 30.38 min. The increase in dissolution rate can be related to the better aqueous solubility of metformin HCl than paracetamol.

Moreover, in comparison to dissolution media of pH 1.2, paracetamol tablets in pH 4.5 and 6.8 and diclofenac sodium in pH 6.8 had sustained releases profile whereas metformin HCl had immediate release profile at same pH values (Fig. 5).

[Figure 5]

However, the MDT was increased with increasing pH values from 4.5 to 6.8 of dissolution medium in case of paracetamol from 529.85 to 3816.35 min and from 4.53 to 15.5 min in case of metformin HCl. Furthermore, the dissolution of diclofenac sodium with MDT of 2000.90 min was faster than paracetamol with MDT of 3816.35 min from SB gel. Consequently it can be recognized that the MDT increased by increasing pH value and the decreasing in aqueous solubility.

The release behavior of different intercalated drugs in SB should be attributed to SB, pH value and the drug solubility that DSC and FTIR proved no interaction between the chemical structure of different drugs and SB.

The visual observation (Fig. 6) for pure bentonite gel tablet revealed that SB formed a structure like a gel in dissolution media at pH 4.5 and 6.8 in case of paracetamol and diclofenac sodium. The FTIR-spectrum of wetted bentonite tablet showed an interaction between Si-OH and $H_2O$ which may be caused by forming hydrogen bonds between water and bentonite structure. However the gel structure of bentonite was proved by Mouzon et al. [19] using scanning electron microscope. This modified the drug release and so extended their release by permeation mechanism. However, the tablets disintegrated in presence of HCl in the dissolution media at pH 1.2 for different drugs and for metformin HCl at different pH values.

[Figure 6]

The sustained release which accompanied gel formation can be hindered in presence of HCl in dissolution media or in the chemical structure in case of metformin HCl and these results come with the reported results of Bendou and Amrani, 2014 that HCl decomposes the structure of bentotie [20].

The suggested application of SB tablets to gain a sustained release can be taken after food or as enteric coated tablets to protect of get destruction effect of low pH effect. However, SB can be applied after food for immediate release.

Sodium bentonite (SB) showed good binding ability and formed robust tablets regarding to their compandial specification. The bad flowability for large scale manufacturing should be overcome using suitable formulation technique such as granulation. According to this study, BS can be a good cheap alternative for common applied excipients such as microcrystalline cellulose (MCC) or lactose. MCC quality and tableting performance varies from different suppliers which limit its application and it is more lubricant sensitive excipient. Furthermore moisture content, particle size, particle shape, bulk density and surface area have a large impact in the MCC compatibility properties [21]. In addition MCC possess a poor flow properties [22]. An alternative of MCC excipients that flow freely but did not disintegrate such as dicalcium phosphate dehydrate [23] or

excipients that flow freely and disintegrate by dissolution such as lactose [24], sorbitol [25], mannitol [25].

## 4. Conclusion:

Sodium bentonite (SB) was applied successfully for preparing tablets for different drugs with different solubility by direct compression on lab scale. However, the bad flowability of 50 % SB mixture was evident which can be the main limitation factor of its applying in direct compression on large scale as it should be improved using appropriate pharmaceutical formulation before it is compressed. According to DSC and FTIR results, SB did not interact with different drugs. Furthermore, SB showed immediate and sustained release for the different incorporated drugs. However, the dissolution behavior of drugs from SB related to the chemical structure and solubility of the drug and pH of dissolution medium. Finally, SB can be used to prepare a sustained release tablets for either of paracetamol and diclofenac sodium.



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Figure 1: DSC thermograms of bentonite (A), diclofenac Na (B), diclofenac Na: bentonite (1:1) mixture (C), metformin HCl (D), metformin HCl: bentonite (1:1) mixture (E), paracetamol (F), paracetamol: bentonite (1:1) mixture (G). Conditions: samples heated from 30 to 210 °C; heating rate: 10 °C/min.

Figure 2: FT-IR spectra of bentonite (A), diclofenac Na (B), diclofenac Na: bentonite (1:1) mixture (C), metformin HCl (D), metformin HCl: bentonite (1:1) mixture (E), paracetamol (F), paracetamol: bentonite (1:1) mixture (G).

Figure 3: Dissolution profiles of, paracetamol in pH 1.2, 4.5 and 6.8 buffered dissolution media (A), diclofenac sodium in pH 6.8 buffered dissolution medium (B), Metformin HCl in pH 1.2, 4.5 and 6.8 buffered dissolution media.

Figure 4: FTIR-spectrum of dry bentonite powder (A), water (B), bentonite gel (C).

Figure 5: Dissolution profiles of Metformin HCl, diclofenac sodium and paracetamol in pH 4.5 and 6.8 buffered dissolution media.

Figure 6: Paracetamol 50% in sodium bentonite tablet after 0 min in dissolution medium of pH 1.2 (A), 10 min in dissolution medium of pH 1.2 (B), 1 h in dissolution medium of pH 6.8 (C), 2 h in dissolution medium of pH 6.8 (D), 24 h in dissolution medium of pH 6.8.

Table 1: The flowabilities of different 50% drug and bentonite mixture.

| | Paracetamol mixture | Diclofenac sodium Mixture | Metformin HCl Mixture |
|---|---|---|---|
| HR | 1.50 ± 0.01 | 1.477 ± 0.07 | 1.41 ± 0.01 |
| CI | 33.24 ± 0.73 | 32.32 ± 2.73 | 29.21 ± 0.67 |

**Table 2.** The estimated areas under curves (AUC) and Mean dissolution times (MDT) of paracetamol, diclofenac sodium and metformin HCl in different pH buffers using phoenix® program, SD Standard deviation of MDT

| Drug | pH | MDT (min) | AUC % released drug*min |
|---|---|---|---|
| Paracetamol | 1.2 | 30.38 ± 2.44 | 146737 |
| Paracetamol | 4.5 | 529.85 ± 68.22 | 68326.6 |
| Paracetamol | 6.8 | 3816.35 ± 2228.91 | 64134.2 |
| Diclofenac sodium | 6.8 | 2000.90 ± 895.2 | 74140.0 |
| Metformin HCl | 1.2 | 16.64 ± 3.14 | 138665 |
| Metformin HCl | 4.5 | 4.53 ± 1.11 | 130550 |
| Metformin HCl | 6.8 | 15.5 ± 4.42 | 134240 |

Figure 1

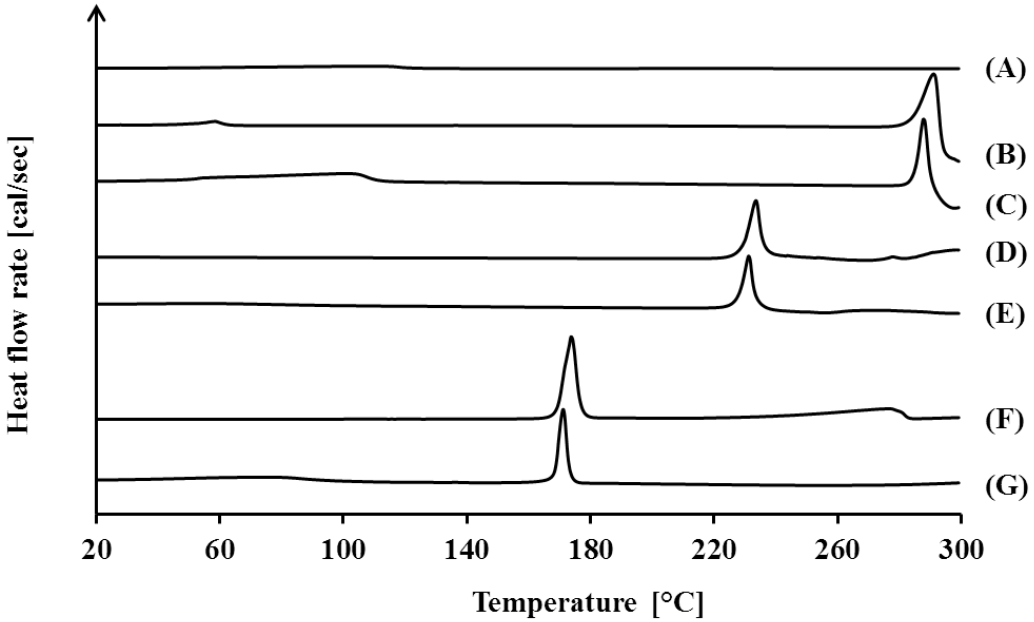


Figure 2

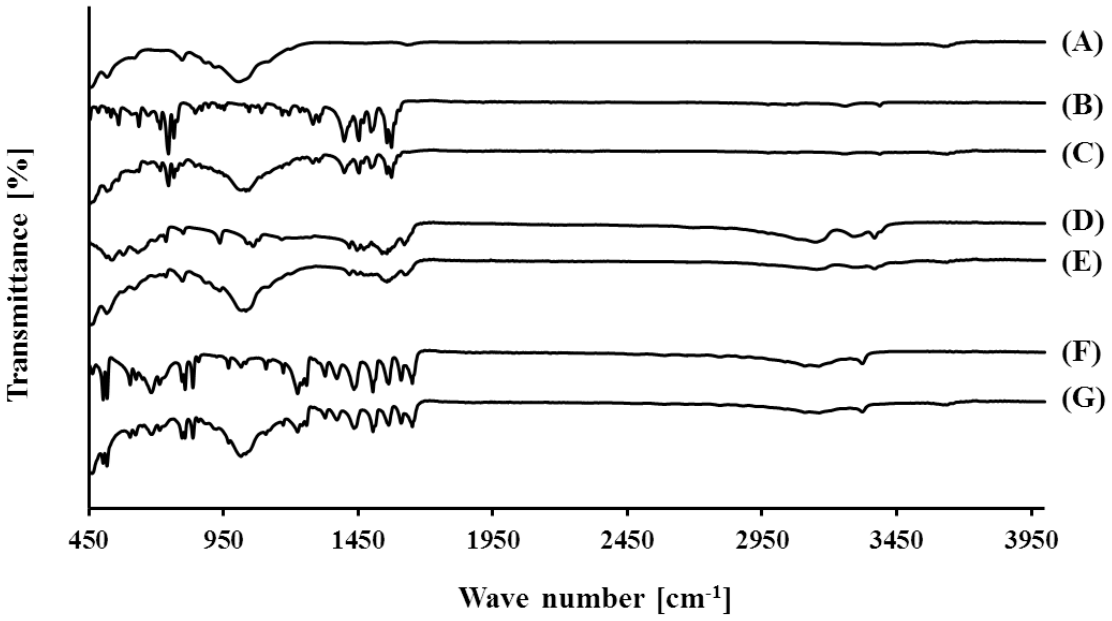



Figure 3

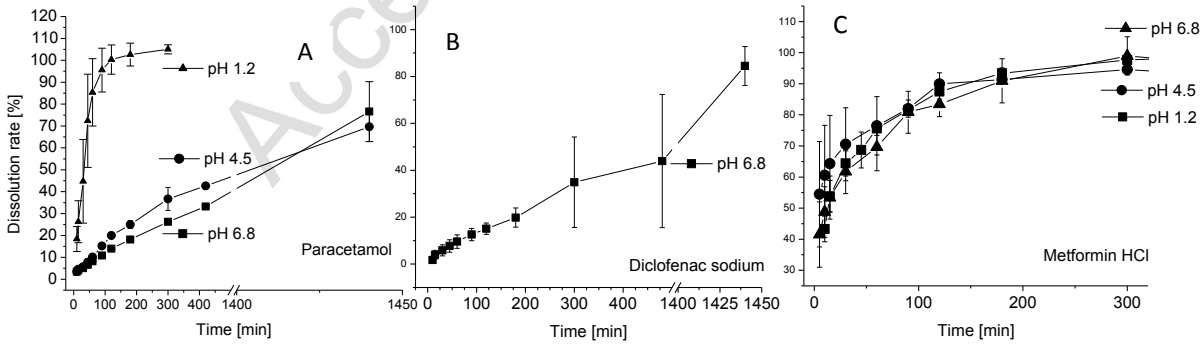


Figure 4

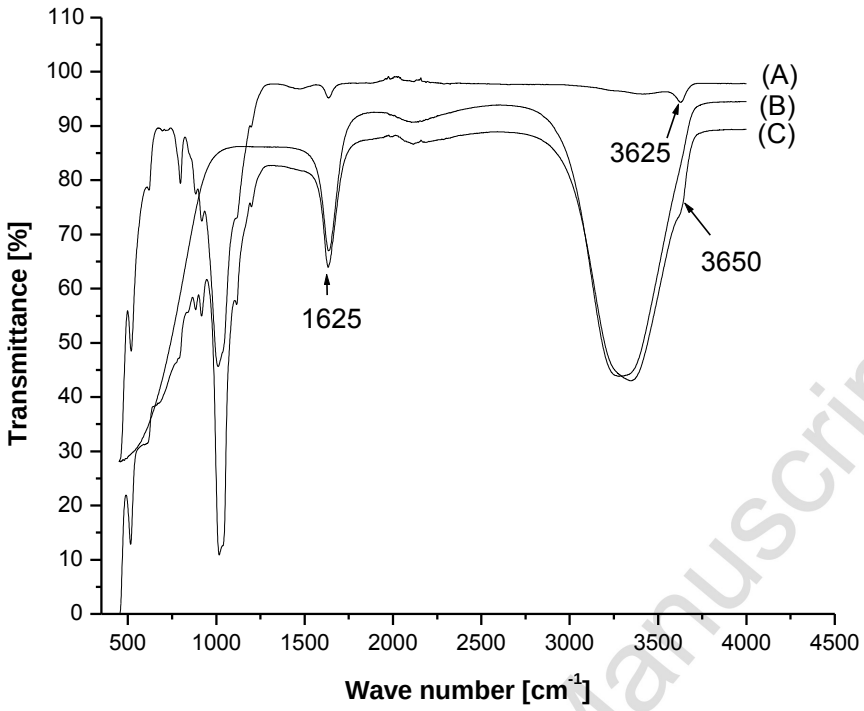


Figure 5

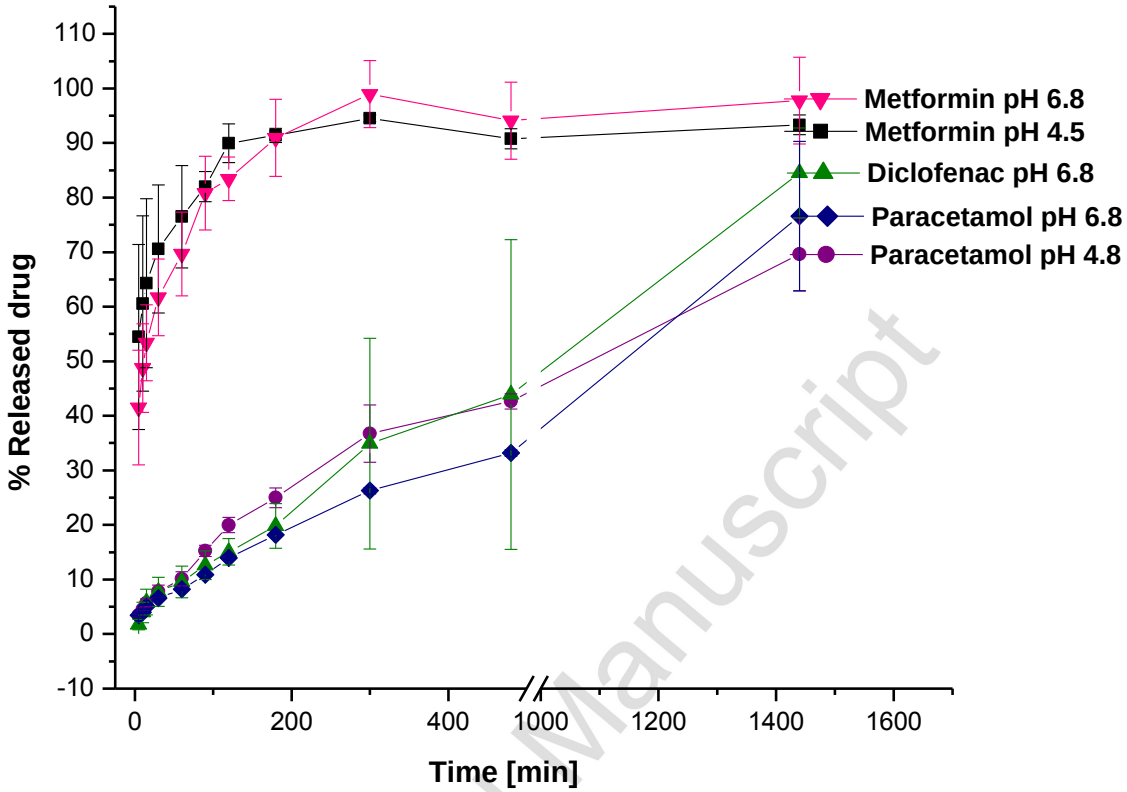
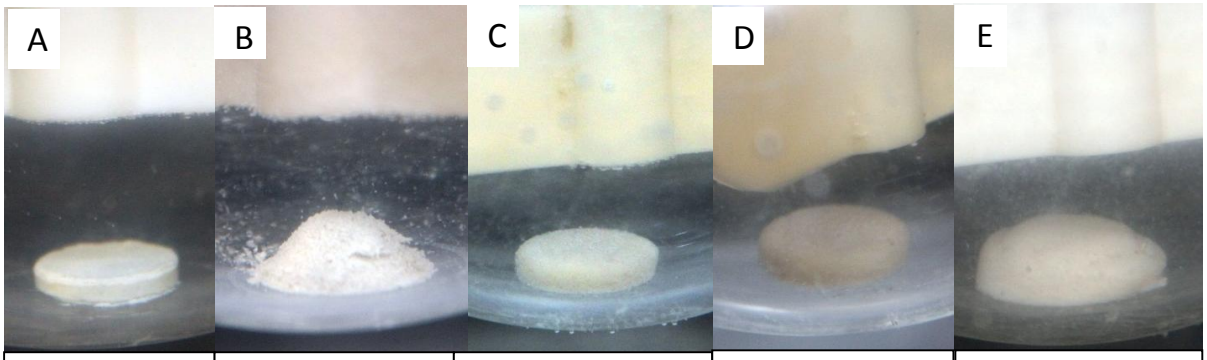


Figure 6




| Paracetamol pH 1.2 at time 0 | Paracetamol pH 1.2 after 10 min | Paracetamol pH 6.8 after 1h | Paracetamol pH 6.8 after 2 h | Paracetamol pH 6.8 after 24 h |
|---|---|---|---|---|