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USING BENTONITE HYDROGEL FOR PREPARATION OF DICLOFENAC SODIUM AND IBUPROFEN SUSTAINED-RELEASE TABLETS

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ABSTRACT

Objective: In this research, bentonite (BEN) was employed to prepare sustained- release tablets of diclofenac sodium (DS) and ibuprofen (IBU) after wet and dry granulation. **Methods:** Granules flowability have been assessed. Also, Fourier Transform Infrared Spectroscopy (FTIR) has been used to determine the drug's compatibility with BEN. The study was conducted to determine the mechanical strength and weight uniformity of the tablets. In both acidic and recommended compendial media, the dissolution profiles were examined. The gel structure of each drug was reduced in an acidic medium, resulting in two enteric-coated tablet formulations for each drug. **Results:** The granules were easily flowable. Furthermore, FTIR spectra revealed no interaction between the drug and BEN. In addition, the formulated tablets met their compendial requirements. According to the data fitting, the drug is released in a fickian manner. Meanwhile, the enteric coating the tablets may preserve their sustained- release behaviour. Even without a binder, the mechanical strength and release behaviour of the tablets remained unchanged. This suggests that BEN is an effective binder on its own. **Conclusion:** BEN has been used successfully to formulate sustained release tablets using both wet and dry granulation methods. When exposed to acidic media, the enteric coating, on the other hand, is critical for protecting the gel structure of BEN.

KEYWORDS: Bentonite, hydrogel, sustained release, tablets.

I. INTRODUCTION

The USP defines colloidal montmorillonite as purified BEN after it has been processed to remove grit and non-swellable compounds.[1] Depending on the concentration, BEN can expand to about twelve times its volume when combined with water, resulting in dense homogeneous suspensions, sols, or gels.[2] Na^+ and Ca^{2+} counter ions hold the negatively charged sheets together in the BEN smectites structure. In the presence of water, these cations tend to hydrate, causing the clay layers to separate in discrete steps.[3]

The body does not take up the hydrated aluminium silicates.[4] BEN can be used without restriction since the FDA's federal code of regulation 21 states that "direct food substances affirmed as generally recognized safe" can be added to food in their pure form.

A technique known as absorbance BEN has been successfully employed to remove harmful impurities from water.[5] In semisolid dosage forms, BEN is used as a suspending agent.[6]

Many researchers are using the gel-forming property to prepare controlled-release tablets. Using olanzapine in montmorillonite dispersed in alginate and xanthan gum biopolymers, Oliveira et al.[7] Garca-Guzmán et al. evaluated the controlled drug delivery system for atorvastatin using gelatin carriers and montmorillonite clay.[8] Wangwang et al. recently studied the release behavior of BEN tablets prepared by direct compression. These mixtures had a poor flowability that limits direct compression.[9]

This study aimed to develop and optimize controlled-release tablets of IBU and DS by using, a gel structure.

II. MATERIALS AND METHODS

Materials

Diclofenac sodium (DS) and ibuprofen (IBU) were purchased from a aljazira pharmaceutical company.

Acetonitrile (HPLC grade) and methanol were purchased from zanju (China). Hydrochloric acid (HCl), microcrystalline cellulose (Avecil PH101) and ortho-phosphoric acid were bought from al-Arabia company (Egypt). Magnesium stearate and Monobasic dihydrophosphate (KH2PO4) were bought from Sigma-Aldrich (Steinheim, Germany). BEN, PEG4000 and PVP40T were bought from Scharlau (Barcelona, Spain). Sodium hydroxide, sodium acetate and glacial acetic acid were bought from Merck (Germany).

Methods

Granulation and tableting

Separately, DS and IBU were ground by a mortar and pestle and sieved through a 45-micron sieve. Binders and DS or IBU were added to BEN in the correct proportions (Table 1) and thoroughly mixed with a mortar and pestle. As a result, the quantity of each ingredient was determined for tablets of 250 or 350mg DS and 800mg IBU. A breakdown of each ingredient's percentage of the tablet's weight (w/w) is indicated in Table 1.

Table 1: Composite of different formulae.

Formulation	DS (mg)	BEN (mg)	Binder (mg)	Lubricant 1% (mg)	Tablet weight (mg)
DS-PVP250	100	130	17.5 PVP (7%)	2.5	250
DS-PVP350	100	222	24.5 PVP (7%)	3.5	350
DS-PEG	100	222	24.5 PEG4000 (7%)	3.5	350
DS-W	100	246.5	-	3.5	350
IBU -MCC5	800	516	70 MCC (5%)	14	1400
IBU-MCC10	800	446	140 MCC (10 %)	14	1400
IBU -W	800	600	-	14	1400
IBU -PEG5	800	516	70 PEG4000 (5%)	14	1400
IBU -PEG10	800	446	140 PEG4000 (10%)	14	1400
IBU-MCC10dry	800	446	140 MCC (10 %)	14	1400
IBU -starch10	800	446	140 Starch (10 %)	14	1400
DS-PVP250	100	130	17.5 PVP (7%)	2.5	250

A pestle and mortar have been used to grind the IBU/MCC mixture into large tablets, then sieved through a sieve of 0.355 mm. The formulated granules were combined by magnesium stearate of 1% and compressed in an Erweka AR 400E single punch tableting machine with an 8 mm die diameter for DS tablets and a 16 mm die diameter for IBU tablets (Heusenstamm, Germany).

Flowability measurement

A 25 mL measuring cylinder was used to determine the volume of ten grams of each powder. The volume was then determined by the previously used cylinder by tapping it 15 times and the bulk density of the used powder was determined by dividing its weight by its volume, whereas the tapped density was determined by dividing the powder's weight by its volume following tapping. According to the US pharmacopoeia 34, three measurements were replicated (USP 34). CAR's index (CI) and Hausner Ratio indicators were then determined using the following formulae (Equations 1 and 2).

$$CI = \left[\frac{Tapped\ density - Bulk\ density}{Tapped\ density}\right] * 100 \ldots\ldots\ldots\ldots$$

Equation 1

$$Hausner\ Ratio = \left[\frac{Tapped\ density}{Bulk\ density}\right] * 100 \ldots\ldots\ldots\ldots$$

Equation 2

Measuring friability

To determine the friability of the prepared tablets, twenty DS tablets and ten IBU tablets were weighed and placed in a friability tester (Erweka TAR20, Heusenstamm, Germany). For 2.5 min, the device was turned on at 40 rpm. After the tablets thoroughly being de-dusted and inspected, the discs were removed and the weights were recalculated using Equation 3 (USP34).

$$\%\ Friability = \left[\frac{WI - WF}{WI}\right] * 100 \ldots\ldots\ldots \textbf{Equation 3}$$

Where WI represents the weight of the tablets before the friability test and WF represents the weight of the tablets after the test.

Measuring hardness

The hardness of various tablet formulations was determined using the Erweka TBH30 (Germany).

Measuring the fourier transform infrared spectroscopy (FTIR)

The compatibility of the drugs with BEN was predicted using an FTIR spectrometer (PerkinElmer UATR Two, Li600301 spectrum manufactured in Llantrisant, UK). Between 450 and 4000 cm^{-1}, the spectra of IBU, DS, BEN, a physical mixture of BEN and each of DS and IBU, water and the granules were measured to determine whether the spectra changed after granulation or in the mixture.

Dissolution test

Dissolution test was determined via USP II dissolution tester (Hanson Research SR6) by measuring the release of the drug from the tablets over 24 h at a rotation speed of 50 rpm and at a temperature of 37±0.1°C. The used volume of phosphate buffers at pH 7.2 and 7.5 for IBU and DS, respectively was 900 ml (USP 34). Time intervals of 1, 2, 3, 4, 5, 6, 7, 8, 16, 20 and 24 h were

used to remove and filter 2 ml samples before being assayed by the HPLC method.

High performance liquid chromatogram (HPLC) assay

Thermo Scientific's Dionex Ultimate 3000 HPLC chromatographic system and diode array detector (Germany) were used to measure the amount of released drugs. A C_8 column from Nanologica, Södertälje, Sweden (250 x 4.6 mm) was used to separate a 100 µl injection volume. Measurement of DS was carried out at a flow rate of 1.5 ml/min and a mobile phase of methanol and monobasic phosphate buffer pH 2.5 (USP 34). IBU was detected at 230nm using a mobile phase composed of glacial acetic of 5ml/l acid with acetonitrile in a ratio of 1:1. The flow rate was 2ml/min.

Enteric coating by using eudragit®

It was coated with Colorcon Opadry-28900 (Pa., USA) (30 g in 200g water 13 %). The weighted tablets had a sub coat content of 3%. The tablets were coated with 12.5 % EUDRAGIT® L 30 D-55 (Evonik Rhon GmbH, Germany). Polymer in aqueous suspension with5% talc (anti tacking) and 1% Triethyl citrate (plasticizer). The atomizing air pressure was set at 1.8 bar, the filter rattling time was set at 5 sec, the filter rattling interval was 30 sec, the drying air volume was set at 90 m^3/h, and the drying air capacity was set at 1.5 m^3/min.kg. With an inlet air temperature of 40°C, an exhaust air temperature of 28°C, and a spray rate of 15g/min.kg, the HI-Coater system was used to perform the process data.[10]

Examination of enteric coated tablets

Dissolving media was 0.1N HCl solutions, and three tablets of each enteric-coated tablet class were dissolved. Temperatures were kept constant at 37°C while the apparatus rotated at 50 rpm. Immediately after 2 h, a sample of each vessel was taken to ensure that the coating was acidic-resistant by testing whether the drug was released from the coat.[11] Then, HCl solution was replaced by phosphate buffer pH 7.2 and 7.5 for IBU and DS, respectively, and samples were measured over 24 h.

Statistical evaluation

The measurements to calculate the averages and standard deviations were carried out three times and the results were assessed for homogeneity by using a t-test with a 95 % confidence interval ($P< 0.05$).

III. RESULTS AND DISCUSSION

HPLC analysis method and calibration curve

HPLC was used to plot a calibration curve for DS dissolution profiles in dissolution medium at concentrations ranging from 0.005 mg/ml to 0.01 mg/ml. The standard deviation of this calibration curve was 2.5%, and the correlation coefficient (r^2) was 0.9994 (Figure 1A). Lowest concentration (0.005 mg/ml) was detected at a much lower concentration than 0.005 mg/ml based on the ratio of peak high to noise high.[11]

The calibration curve for IBU, on the other hand, was established for concentrations ranging from 0.1 to 8 mg/ml, having a correlation value (r^2) of 0.99995 and a standard deviation of 4% (Figure 1B).

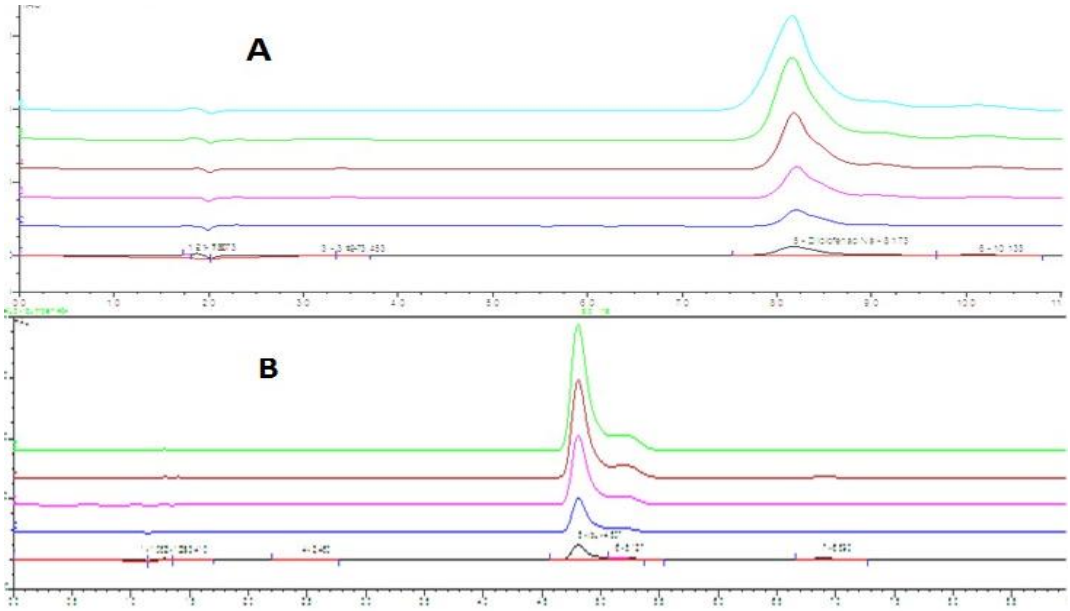

Figure 1: HPLC chromatograms of A: DS; B: IBU.

Flowability of granules

Because granules have a higher weight and a lower specific surface area than separate particles, they have good flowability.[12] A measuring cylinder was used to determine the bulk densities of dry granules. The measuring cylinder was tapped 15 times across the horizontal surface and the tapped density was determined. From tapped density and bulk density each of Hausner and CAR's indexes were determined, as shown in Table 2.

Table 2: The estimated flowabilities using CAR's index and Hausner ratios*.

Formulation	CAR's index %	Hausner ratio
DS-PVP250	10.11± 0.29	1.02 ±0.07
DS-PVP350	10.53 ± 0.3	1.03 ±0.06
DS-PEG	6.69 ± 0.14	1.05 ±0.08
DS-W	10.63 ± 0.8	1.02 ± 0.12
IBU -BEN not granulated	28.06 ± 0.07	1.22 ± 0.019
IBU -MCC5	13.13 ± 0.32	1.01 ± 0.35
IBU -MCC10	14.59 ± 0.32	1.12 ± 0.021
IBU -W	19.42 ± 0.54	1.12 ± 0.067
IBU -PEG5	14.75 ± 0.23	1.02 ± 0.045
IBU -PEG10	13.41 ± 0.25	1.07 ± 0.035
IBU -MCC10 dry	8.98 ± 0.22	0.11 ± 0.034
IBU -starch10	7.2 ± 0.25	1.05 ± 0.037

*** Results are represented as mean ± SD, n = 3.**

The flowability of the physical mixture of DS and BEN was poor.[9] The measured flowability of the physical mixture of IBU and BEN in Table 2 also revealed a poor flowability of this mixture. The results in Table 2, on the other hand, showed that flowability improved after granulation.

FTIR-spectra

Figure 2A shows the FTIR spectra of various components, hydrated tablets and granules of DS, and Figure 2B shows the FTIR spectra of IBU.

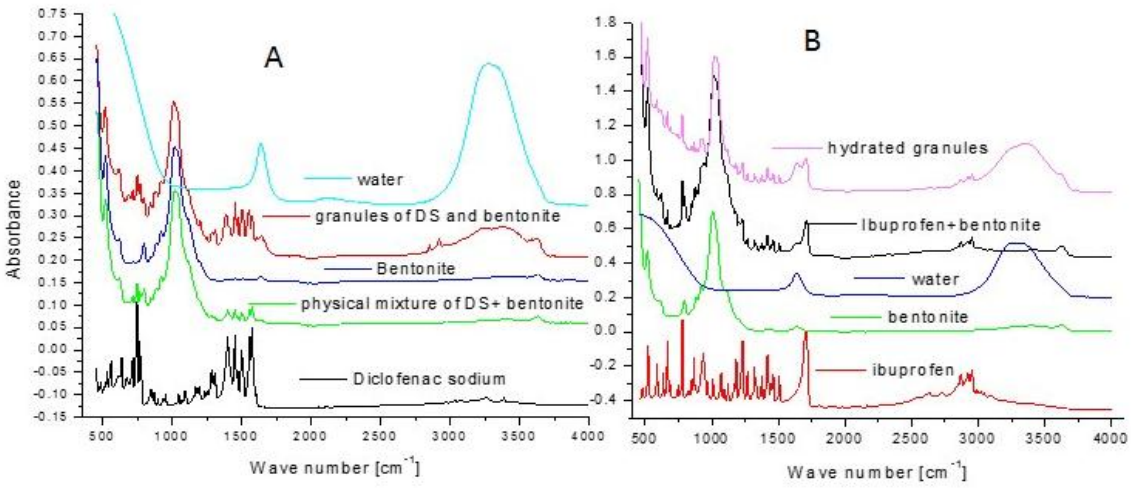

Figure 2: The FTIR spectra of A: pure DS, BEN, water, BEN physical mixture, and DS granules formulated by water; B: pure IBU, BEN, water, IBU granules formulated by water, and IBU hydrated granules formulated by water.

In the FTIR spectrum of water, broadband at wave number between 3000–3700 cm^{-1} and a band appeared at 1625 cm^{-1}, linked to O–H stretching and bending vibrations, respectively. According to BEN's FTIR spectrum, the stretch vibrations of Si-O in the tetrahedral sheet are reflected in a band at 1021cm^{-1}. Si-O-Al (octahedral sheet) and Si-O-Si bend vibrations are responsible for the 524 and 464 cm^{-1} bands.[13]

Granules have been found to have a stretching O–H water band at 3000–3700 cm^{-1} after drying, which indicates that the granules are still moist. When water is added to the BEN tablet, the intensity of the Si-O stretch vibrations in the Si-O-Si groups at 1021cm^{-1} decreases, indicating that there is water present in between the BEN sheets, while the H_2O was bending vibrations at 1625 cm^{-1} increase. However, there was no evidence of a shift

in the spectra of the granules other than the bands of the components used in their production, indicating that the drugs and the components used have no interaction. The drugs' compatibility with BEN was demonstrated by their FTIR spectra.

Quality control of tablets

When the tablets were compressed, they were tested for hardness and friability, and the obtained results are showed in Table 3.

Table 3: The hardness and friability of formulated tablets*.

Formulation	Hardness (N)	Friability %
DS-PVP250	150± 4.3	0.36± 0.02
DS-PVP350	125 ± 6.5	0.15 ± 0.03
DS-PEG	108± 4.4	0.3± 0.02
DS-W	122± 5 .5	0.37±0 .05
IBU -MCC5	245.5 ± 4.5	0.39 ± 0.02
IBU -MCC10	249.5 ± 8.6	0.22 ± 0.03
IBU -W	346 ± 8.2	0.28 ± 0.03
IBU -PEG5	274.5 ± 4	0.45 ± 0.02
IBU -PEG10	252.6 ± 5.2	0.4 ± 0.01
IBU -MCC10dry	205.1± 14	0.4 ± 0.02
IBU -starch10	194.3 ± 5	0.25 ± 0.03

*** Results are represented as mean ± SD, n = 3.**

The compressed granules had a high degree of hardness, which ensured that the tablets would not disintegrate quickly when they came into contact with the buffer.[14] There was also a correlation between mechanical strengths of the different tablets, both with and without a binder, which indicates that the interaction between BEN - BEN plays a major role in binding forces. After drying hydrated BEN clay, Kawatra and his colleagues demonstrated a clay bonding film using fibres woven on glass shot. Additionally, conventional iron ore mixing did not produce BEN fibres in the iron ore pellets.[15]

Friability and weight uniformity results showed that the tablets met pharmacopeial standards. The strength of the formulated tablets, regardless of binder or weight, was higher in IBU tablets than DS tablets, and this strength increased as the weight of the tablets increased.

Dissolution behavior of uncoated tablets

Aid PVP (a binder) was first used to prepare 100mg DS tablets weighing 250mg. Weighting tablets up to 350mg was necessary to slow DS release by increasing the fraction of BEN, because this tablet released relatively quickly. PVP and PEG4000 were used as binders, and water alone was used to make the tablets. Binders for 800mg IBU tablets included microcrystalline cellulose (Avecil®PH102), PEG4000 at 5 and 10% concentrations, and starch at 10% concentration. In addition, the granules used to make the IBU and BEN tablets were made without the use of a binder. Hence, HPMC was used as a gel builder rather than a binder in the formulation of sustained- release tablets[16], in order to avoid any potential influence on the results. Also, the binders that were tested and failed to build gel structures of BEN were not mentioned in this study. Over the course of 24 h, HPLC methods were used to estimate the concentrations of DS and IBU in the dissolution vessel. In addition, the release profile of a commercial reference was examined under similar conditions. As in figure 3A and B, the dissolution behaviors of various types of formulated tablets were calculated by using the cumulative released amount as a percentage versus the passage of time.

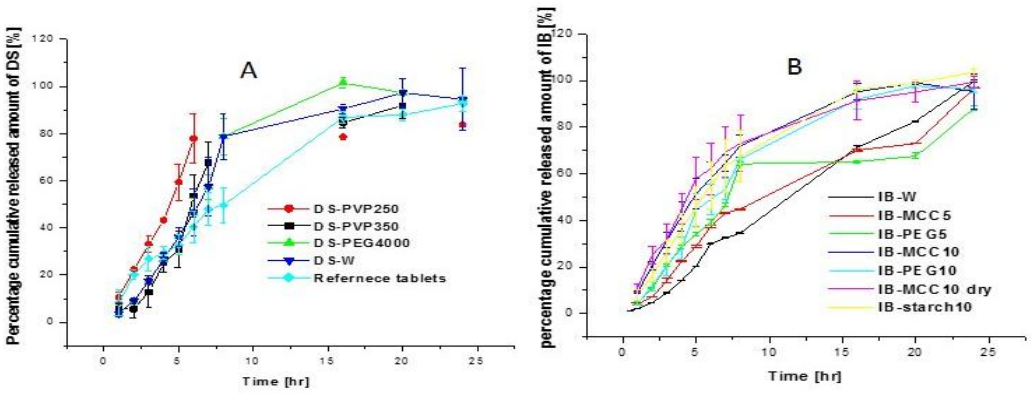

Figure 3: Dissolution profiles of A: DS from different formulated tablets; B: IBU from different formulated tablets.

A number of correlation coefficients (r) were determined from the release profiles of various formulated tablets by fitting each released quantity against time, the route squared of time (fickian release), and the logarithm of percentage released quantity versus time (first order).[17] The results are listed in Table 4.

Table 4: The correlation coefficient of zero order, first order and Fickian diffusion*.

Formulation	Zero order	Zero order over 24 h	First order Over 24 h	Fickian diffusion over 24 h
DS-PVP250	0.999±1.49 over 6 h	0.786± 18.6	0.686± 0.25	0.870 ± 14.9
DS-PVP350	0.985±1.83 over 16 h	0.919± 14.1	0.798 ± 0.31	0.956 ± 10.6
DS-PEG	0.994±1.49 over 16 h	0.901± 16.7	0.765 ± 0.32	0.950 ± 11.9
DS-W	0.979 ±3.67 over 16 h	0.906 ± 15.7	0.763 ± 0.32	0.956 ± 10.6
Reference	0.978 ±2.22 over 16 h	0.981± 6.1	0.976 ± 0.06	0.964 ± 8.41
IBU -MCC5	0.977 ± 29.2 over 24 h	0.977 ± 29.2 over 24 h	0.826± 0.26	0.990 ± 4.32
IBU -MCC10	0.985±1.80 over 16 h	0.908± 13.6	0.766 ± 0.217	0.966 ± 8.40
IBU -W	0.996± 2.94 over 24 h	0.996 ± 2.94	0.844± 0.35	0.983 ± 6.5
IBU -PEG 5	0.993 ± 4.77 over 8 h	0.915 ± 11.2	0.763± 0.26	0.957± 7.9
IBU-PEG 10	0.996 ± 0.83 over 8 h	0.934± 12.63	0.773± 0.28	0.966 ± 8.4
IBU-MCC10dry	0.991 ±0.59 over 8 h	0.899± 13.593	0.759 ±0.20	0.961 ± 8.6

*** Results are represented as mean ± SD, n = 3.**

As determined in Table 4, the release of cumulative released quantity versus time of various tablets represented a correlation coefficient more significant than 95% in the first 16 h, indicating that the release rate is constant in the first 16 hours and then decreases as the line becomes non-linear.

The estimated correlation coefficients in Table 4 are greater than zero when calculated for prediction fickian diffusion than for prediction first order, indicating that the drug is released from the gel matrix via fickian diffusion. Tablets prepared by granulation were subjected to 0.1N HCl to mimic the passage of prepared tablets through the GIT. The tablets were unable to withstand the HCl solution and disintegrated over a while. As a result, enteric coating was required to protect the tablets from HCl. Enteric-coated enteric-coated tablets were selected for each drug based on its linearity. Two hours of exposure to 0.1 N HCl was all that was required to deactivate the coatings. Samples were taken from the acidic media after two hours to see if the coating was resistant to the acidic environment. A phosphate buffer solution (pH 7.5) was used to replace the acidic media, and sampling was conducted for another 24 h. Figures 4 depict the findings.

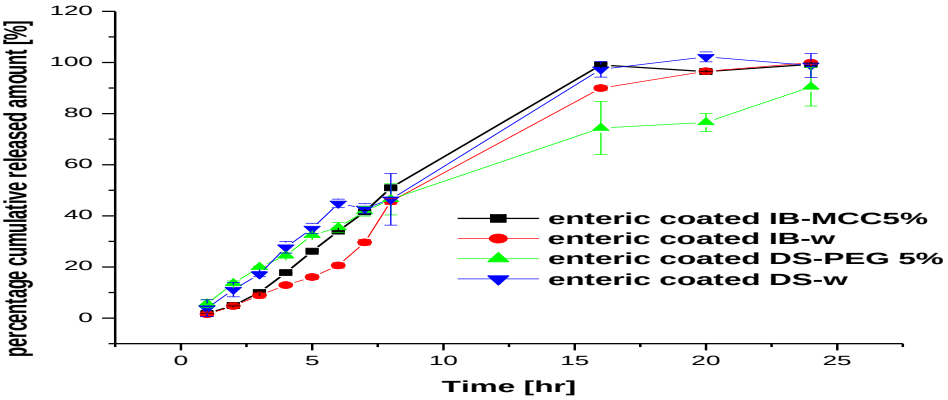

Figure 4: A: Dissolution patterns of DS from various tablet formulations; B: IBU from various tablet formulations.

Enteric-coated tablets containing DS and IBU were first immersed in HCl 0.1N for 2 hours before being immersed in phosphate buffer pH 7.5 for 24 h.

In the acidic media, the enteric coat of formulated tablets is resistant for 2 h to the acids, and neither DS nor IBU were detected.

After taking the extended release tablet, the drug is released over a longer period of time. To ensure compliance with USP34, the extended release DS tablets' DS release percentages must be between 15 and 35 percent, 45 to 65 %, 65 to 85 %, 75 to 95 %, and at least 80 % after 1, 5, 10, 16, and 24 h, respectively. This means that the prepared DS tablets meet the requirements of the test. It is possible that DS sustained-release tablet tests 2 through 4 could be met if the release is faster.[18] After taking the extended release tablet, the drug is released over a longer period of time. To ensure compliance with USP34, the extended release DS tablets' DS release percentages must be between 15 and 35 %, 45 to 65 %, 65 to 85 %t, 75 to 95 %, and at least 80 % after 1, 5, 10, 16, and 24 h, respectively. This means that the DS tablets that have been prepared meet the requirements of the test. It's possible that DS sustained release tablet tests 2 through 4 could be met if the release is faster.[19] Since the gel structure is thought to be the cause of drug retention in tablet matrix and slow diffusion into dissolution medium, it can be assumed that the gel structure is the culprit (Figure 5).

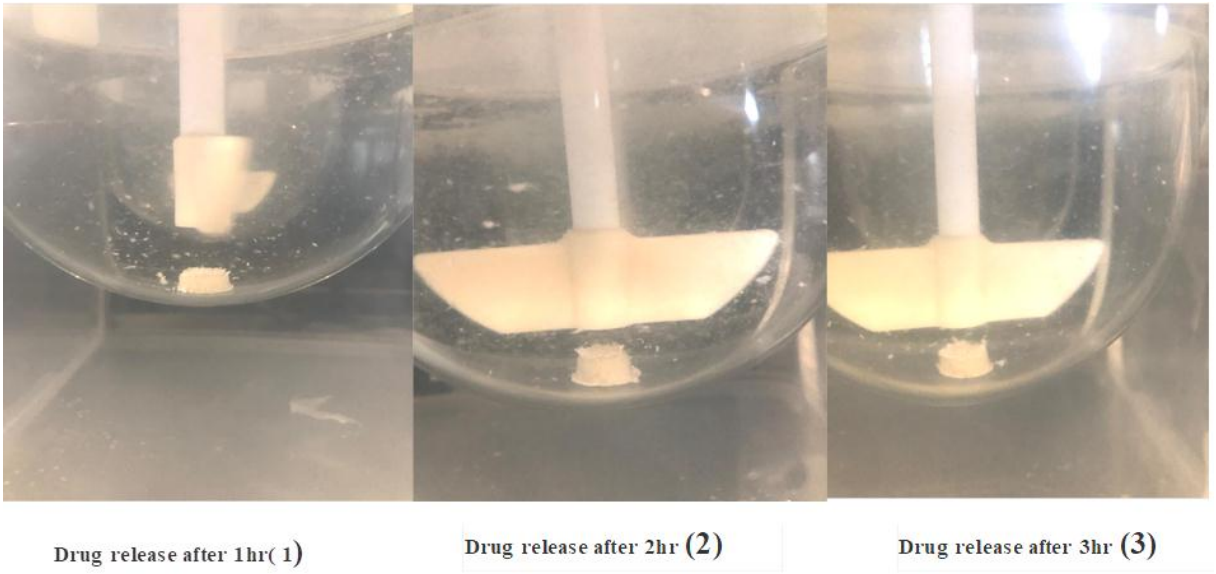

Figure 5: Gel structure of BEN tablets in phosphate buffer, pH 7.5.

Binders appear to have no effect on the diffusion of the gel matrix prepared tablets by wet or dry granulation compared to those prepared without any binder. According to Tables 3 and 4, hardness isn't being reflected by a decrease in the release of DS or IBU. Due to diffusion through gel structure, rather than erosion of structure, release slowed. For IBU tablets prepared without a binder, zero-order correlations were higher than fickian diffusion correlations for zero-order correlations. This shows that gel structure is better without a binder in place. Because hydrochloric acid breaks down the gel structure, the release behavior was

affected. Along with findings from Bendou and Amrani, the presence of hydrochloric acid inhibits the gel formation of BEN in aqueous media, leading to tablet disintegration.[20] As a result, BEN was shielded from the acidic media by the enteric coating on the tablets. 0.1N HCl was successfully resisted by the enteric coated tablets for two hours. In addition, the release profile of the selected reference was similar to the dissolution profile of the enteric coated DS tablets in dissolution medium at pH 7.5. It was found that the release percentages in acidic medium after 1, 4, 7 and 16 h were 39, 60 and 70 % respectively which met the requirements of the USP34 test 4 for extended-release DS tablets.[21]

Gel builder polymers such as hydroxyl propyl methyl cellulose (HPMC) are more expensive than BEN for making sustained release tablets.[16] In addition, increasing the pH at the absorption site and improving absorption are two ways that the basic pH of BEN can improve the solubility of DS and IBU.[22] Even though there is a chance that the enteric coating can help improve patient compliance, it is not without risk.

IV. CONCLUSION

BEN was found to be a viable ingredient in the formulation of sustained-release DS and IBU tablets. It has been also found that BEN acts as a binding agent in preparing tablets and providing mechanical strength comparable binders used to prepare tablets. Granulation can be used to improve the flowability of BEN mix, which is helpful for large-scale manufacturing. Enteric coating also prevented the degradation of gel structure of BEN in acidic media. Bioavailability of the formulated tablets can, however, is supported by further in vivo studies.

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