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Enhancing the Solubility of Phenylbutazone Using Novel Syloid Silica (AL-1FP) Formulation

Attahiru Sabiu[1]*, Ahmad Shamsudeen Abdullahi[1], Yusuf Amina Jega[2], Yunusa Buhari Idris[1], Umar Bashar[1]

[1]Faculty of Science, Department of Pure and Industrial Chemistry, Sokoto State University, Sokoto, Nigeria
[2]Faculty of Pharmacy, Department of Medicinal and Pharmaceutical Chemistry, Usmanu Danfodiyo University, Sokoto, Nigeria

(*) Corresponding author: sabiuattahiru@gmail.com mobile no +2347068237030

Abstract

The purpose of this study was to use silica-based formulations to improve the solubility and rate of dissolution of phenylbutazone, a medication that is poorly soluble in water. Using a solvent-free process that involved hydration, heating, and drying, Syloid silica (AL-1FP) was used to create solid dispersions at drug-to-excipient ratios of 1:1, 2:1, and 1:3. The formulations were characterized using dissolution testing, Fourier Transform Infrared Spectroscopy, X-ray diffraction, Differential Scanning Calorimetry, and Scanning Electron Microscope. The results confirmed the drug's transition from crystalline to amorphous states, and pore entrapment in the silica matrix markedly improved dissolution. The most significant promotion was experienced with the 1:3 ratios, which released 98.9% of phenylbutazone after 45 minutes compared to 31.9% for the pure medication. This illustrates the effectiveness of Syloid silica in overcoming the solubility limitations of BCS class II drugs, providing a scalable approach for veterinary formulations.

Keyword: Solubility, Phenylbutazone, Syloid silica, Drug, Dissolution.

Introduction

The solubility of active pharmaceutical ingredients (APIs), especially hydrophobic ones, is a critical challenge in formulation for effective drug delivery [1-3]. Poor water solubility leads to low dissolution rates in the gastrointestinal tract, causing unpredictable absorption and incomplete bioavailability. Many new orally administered drugs exhibit solubility problems due to high lipophilicity, complicating formulation development. Solubility is defined as the maximum solute concentration dissolvable in a solvent under constant conditions [4]. Solubility is defined as the characteristic property of solute to dissolve in a solvent, forming a homogeneous solution at dynamic equilibrium. It is expressed in various concentration units, with Log P

measuring differential solubility in octanol and water to indicate hydrophobicity.

Pharmacopoeias like BP and USP categorize solubility by solvent components. The ICH M9 guideline defines a drug as highly soluble if its highest dose dissolves completely in ≤250 mL of aqueous media across a pH range of 1.2-6.8 at 37 ± 1°C. Permeability, the ability of a drug to pass through a membrane, is mathematically defined by its diffusion coefficient across the membrane, multiplied by its partition coefficient, and divided by the membrane's thickness. It is crucial for therapeutic efficacy; as low permeability can lead to an ineffective response.

The Biopharmaceutics Classification System (BCS) categorizes drugs into four classes (I-IV) based on their aqueous solubility and membrane permeability, factors vital for bioavailability [5]. Class I drugs exhibit high permeability and high solubility (e.g., Propranolol). [6-8]. Class II drugs have high permeability but low solubility, with dissolution rate limiting absorption (e.g., Ketoprofen). Strategies to enhance solubility for these drugs include amorphization, nanoparticles, and co-crystals. [9]. Class III drugs possess low permeability and high solubility, where absorption is limited by permeation rate (e.g., Ranitidine). Class IV drugs are characterized by both low permeability and low solubility, typically resulting in poor absorption and variable pharmacological response (e.g., Furosemide). The Biopharmaceutical classification system CS framework, established by factors like solubility and permeability, is utilized by regulatory agencies such as the USFDA, EMA, and World Health Organization for drug approvals, aiding in drug product development. A drug is considered highly soluble if its highest dose strength dissolves in 250 mL or less of aqueous media across a pH range of 1 to 7.5. Permeability is indirectly assessed by the extent of human absorption via mass transfer rates across the intestinal membrane [10-12].

Phenylbutazone

The active pharmaceutical ingredient, phenylbutazone (1,2-diphenyl-4-n-butyl-3,5-pyrazolidinedione), is mostly utilized in non-steroidal anti-inflammatory medications to alleviate pain related to chronic musculoskeletal disorders, including arthritis. Additionally, it has analgesic and antipyretic properties [13-15].

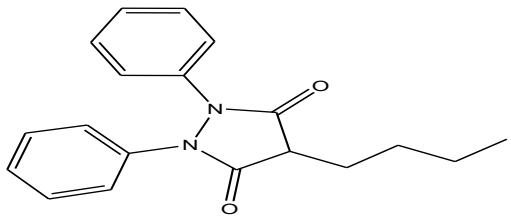

Figure 1: Chemical Structural of Phenylbutazone

Phenylbutazone, first commercialized by Geigy in 1952 as Butazolidin, is synthesized using malonic acid ester. Its use in humans has been restricted in several countries due to bone marrow toxicity, though it remains in veterinary applications, particularly for horses. Phenylbutazone readily forms solvates and

exhibits polymorphism, with at least three polymorphs achievable through evaporative solvent crystallization and additional forms via grinding and spray-drying.

The delta form is generally recognized as the product of heating other polymorphic forms, though the precise nature of these transitions, including whether they involve melting and recrystallization, lacks consistent description. Transitions are reportedly irreversible, with no retransition from the delta form to other polymorphs observed after initial transformation [16]. While melting phenylbutazone produces a wax-like, largely amorphous substance, typical crystallization from organic solutions yields highly ordered polymorphic forms.

Phenylbutazone exhibits poor water solubility but dissolves in various chemical solvents and aqueous buffer solutions, with its solubility in phosphate buffers extensively studied. Its well-examined solubility parameter allows prediction of solubility across many common solvents using the Hildebrand, Prausnitz, and Scott methodology [17].

Phenylbutazone, a nonsteroidal anti-inflammatory medication (NSAID) utilized in equine pain management, presents formulation challenges due to its low water solubility, impacting dissolution and absorption. Despite some success with polyethylene glycol 8000 solid dispersions, improved release of the active component is still desirable, particularly as current formulations often exhibit poor palatability and administration issues [18,20].

This study investigates Syloid silica-based excipients for their potential to accelerate phenylbutazone dissolution. Mechanisms for improvement include drug adsorption into silica pores, conversion to an amorphous state, and increased surface area. While Syloid silicas are known for improving powder flow, their capacity to enhance dissolution has seen limited prior exploration with other model drugs, suggesting a need to further assess their applicability for phenylbutazone, given its critical use and formulation limitations [21].

Materials and Methods

Materials

Phenylbutazone ($C_{19}H_{20}N_2O_2$) was obtained from Sigma-Aldrich while dipotassium hydrogen phosphate (K_2HPO_4 - purity 98 %) and potassium dihydrogen phosphate (KH_2PO_4 - purity 99 %) were kindly donated by the Chemistry Laboratory, Sokoto State University, Sokoto. Silica AL 1FP (pore size 10 µm, surface area of 605 m^2g-1 and pore volume 0.23 mL/g) was supplied by Sigma-Aldrich.

Methods

A sample mass of 200 mg of Syloids silica AL-1FP and 40 mL of buffer solution was gradually added, followed by 200 mg of phenylbutazone to achieve a total drug and silica mass of 400 mg. The solution was stirred Over a period of 60 min

and heated to a maximum of 90°C, cooled to room temperature, vacuum filtered and dried over night at 60°C, and then sieved to remove agglomerates larger than 250 mm. The process was repeated with the replacement of PhB and AL-1FP 1:1 with of PhB and AL-1FP 2:1 and of PhB and AL-1FP 1:3 ratios to produce a total of three unique drug-Syloids silica formulations. Buffer solution was used as a 'carrier' to disperse the drug within the mixture, rather than dissolving the drug with organic solvent.

Wavelength determination (λmax)

To determine the λ max of Phenylbutazone, a stock solution containing 100 µg/mL of phenylbutazone was made in phosphate buffer (p^H 6.94). The solution was then sonicated for an hour using a VWR-USC 300T. The wavelength of maximum absorption in the 200–800 nm region was then measured using a Cary 60 UV/Vis spectrophotometer after a reference solution of 25 µg/mL had been produced in a 25 mL volumetric flask

Calibration Curve for phenylbutazone at 228 nm

Stock solutions of phenylbutazone (0.2–2.0 mL) were pipetted out into a series of eight volumetric flasks of 10 mL. The volume in each volumetric flask was made up to the mark with buffer solution; it produced the concentration range of 0.2-1 µg/mL of phenylbutazone. The absorbance of the solution was measured at 228 nm against buffer solution.

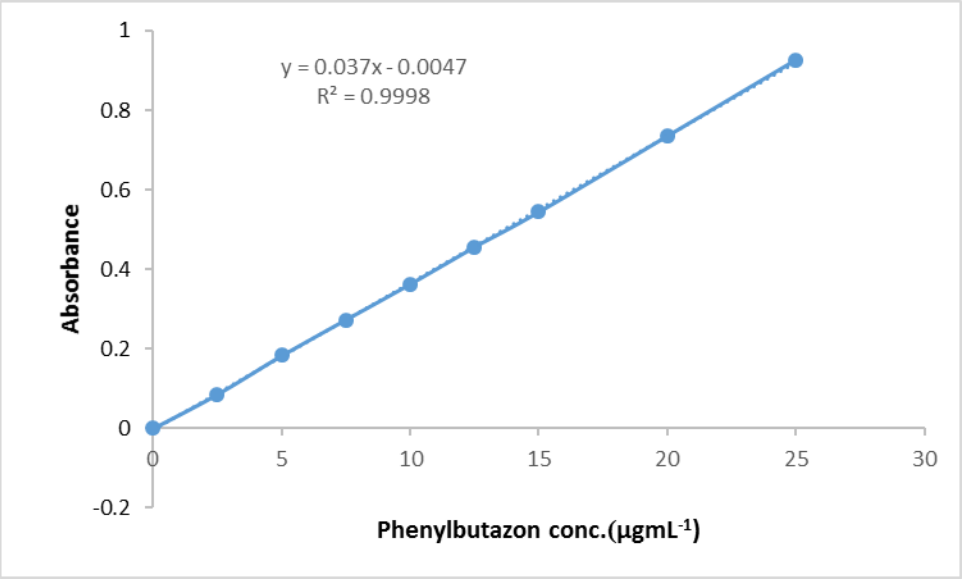

Figure 2: Phenylbutazone calibration plot

Characterization methods

Powder X-ray diffraction (XRD) data were collected on a Bruker D2-Phaser equipped with a Cu Kα1 radiation source at 30 kV and 10 mA current. Particle size distribution of the formulated products was analyzed using a Malvern Master sizer 2000 (Worcestershire, UK) using 5–10 mg of powder per sample with one drop of surfactant (IGEPALs CA-630) at a stirring speed of 2000 rpm.

Triplicate data was subsequently analyzed using Mastersizer2000 software (V5.61). Drug loading was verified to be 100% in all formulated samples by UV analysis of the filtrates (λ = 282 nm) with no residual drug detected (< 1%), thus confirming all of the drug remained within the formulation (rather than being washed away with the filtrate during the formulation process). For stability confirmation, the infrared spectrum for the pure samples and their formulations was recorded using a Nicolet-380 Fourier Transform Infrared spectrometer (FT-IR) with an ATR crystal.

Powder samples were placed directly onto the diamond crystal, and the anvil was lowered to ensure that the sample was in full contact with the diamond. Each spectrum was obtained in the range of 500–4000 cm^{-1} with 2 cm^{-1} resolution. In this study, the morphology of pure phenylbutazone and with different ratios of silica was performed with a Keyence microscope (VHX-2000) equipped with a microscope real zoom lens (RZ x200-x2500). The magnification range was between 200 and 2500, and samples of 2 - 4 mg of each powder were put on the microscope slides (1 mm thickness, 76 x 26 mm dimensions) with a cut, ground edge and without a frosted marking area. The images were obtained on a 3D display.

***In vitro* phenylbutazone release**

Dissolution tests were carried out using Hanson research SR8-Plus dissolution apparatus, Using a thermostat bath. A (USP 2) paddle method was used at a temperature of 37.0 ± 0.5°C and a rotational speed of 75.0 rpm. To eliminate the air bubbles, the buffer-containing containers were sonicated for ten minutes. Samples containing 22.5 mg of total medication were put in vessels with 900 mL of buffer. Using a Carry 60 UV/Vis spectrophotometer, aliquots of 5 mL were taken out of each of the two vessels at regular intervals starting at 5 min and continuing for 45 min set at a wavelength (λ) of 282 nm with conversion to percentage drug release using a standard calibration plot. Measurements were made in triplicate on pure phenylbutazone and phenylbutazone-loaded silica.

Concentrations in the liquid samples were analyzed using the equation of the graph and the mean of the percentage of drug release and their corresponding standard deviations were calculated

Results and Discussion

Material characterization

The XRD pattern for pure phenylbutazone displays the sharp peak predicted for a crystalline solid, the XRD pattern is featureless, for silica since silica is amorphous, for the formulation based on phenylbutazone and silica AL-1 FP, few small XRD peaks caused by nanocrystals were visible, and adding various forms of silica reduced the proportion of crystalline phenylbutazone. Kakala *et al.* (2017) [13] stated that when there are no distinctive peaks for drug after incorporating it with mesoporous silica, it can be deduced that the drug is absorbed in the pores and on the surface of mesoporous silica as shown in Figure 3.

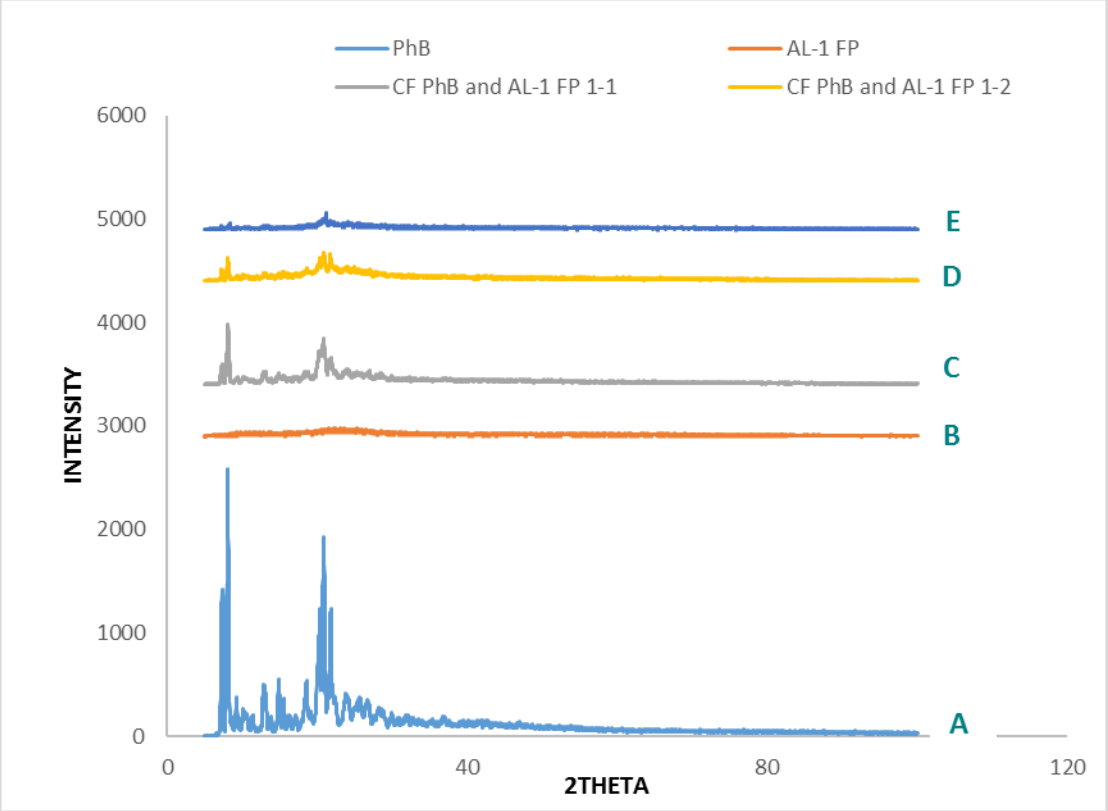

Figure 3: XRD scan of pure phenylbutazone, AL-1 FP and phenylbutazone loaded silica AL-1 FP with three ratios (1:1, 2:1, and 1:3) (a) phenylbutazone (b) AL-1 FP (c) CF PhB and AL-1 FP 2:1 (d) CF PhB and AL-1 FP 1:3

FT-IR spectroscopy was used to monitor the presence of phenylbutazone and determine interactions with the silica. Analysis of spectra for phenylbutazone showed the expected absorption bands at wavenumbers (with corresponding functional groups) of 754 and 1483 cm^{-1} (C-H), 1270 cm^{-1} (C-N) and 1720 cm^{-1} (C=O). Analysis of the spectra for phenylbutazone subjected to the processing method did not reveal any changes in the specific absorption bands for the drug,

suggesting a lack of degradation as a result of the formulation process. The three phenylbutazone Syloids silica's ratio,1-1,2-1, and 1-3 of AL-1 FP were analyzed using FT-IR spectroscopy and all displayed the expected intense Si-O absorption band at 1060– 1070 cm^{1}. For the three phenylbutazone-silica formulated products, the results indicated a significant disappearance of the drug, mainly displaying spectra corresponding to just each type of drug silica ratio present. Furthermore, the spectra did not display any obvious additional peaks, thus indicating there had been no significant changes in the chemical structure or drug-silica interactions.

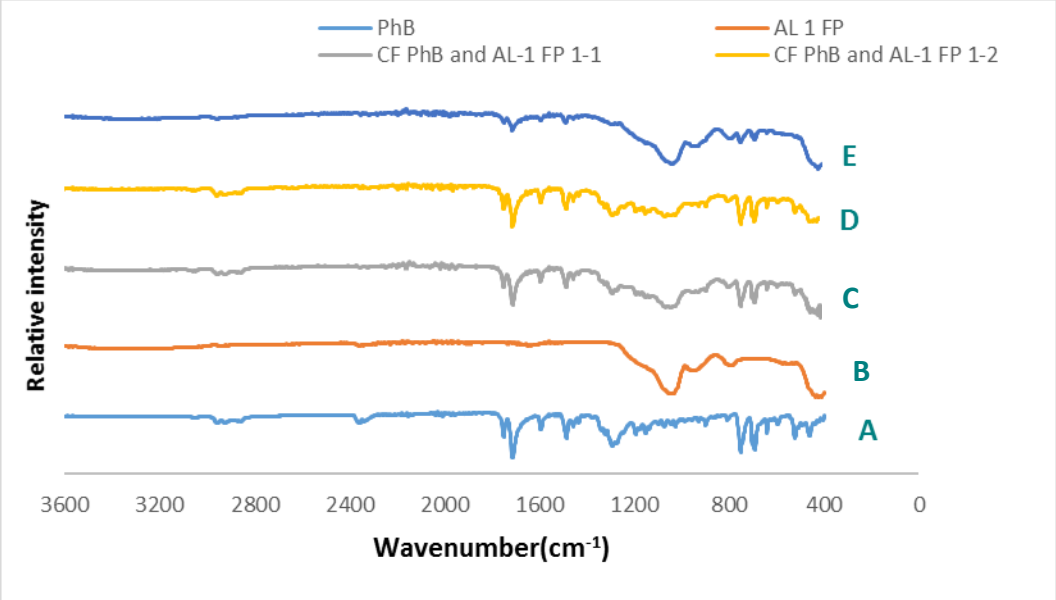

Figure 4: FT-IR analysis of phenylbutazone, AL-1 FP, and phenylbutazone with AL-1 at different ratio (1:1, 1:2. And 1:3) (a) phenylbutazone (b) AL-1 FP (c) CF PhB and AL-1 FP 2:1 (d) CF PhB and AL-1 FP 1:3

Surface morphologies of the pure phenylbutazone and, and Syloids silica-based formulations –AL-1 FP are presented in Figure 5. The drug's crystalline state, along with the disordered irregular shapes of AL-1 FP, The SEM image confirmed the insignificant effect of processed phenylbutazone as the drug retained a crystalline structure. However, there was a uniform distribution of phenylbutazone on the surface of AL-1 FP due to a larger surface area, smaller pore volume and pore diameter.

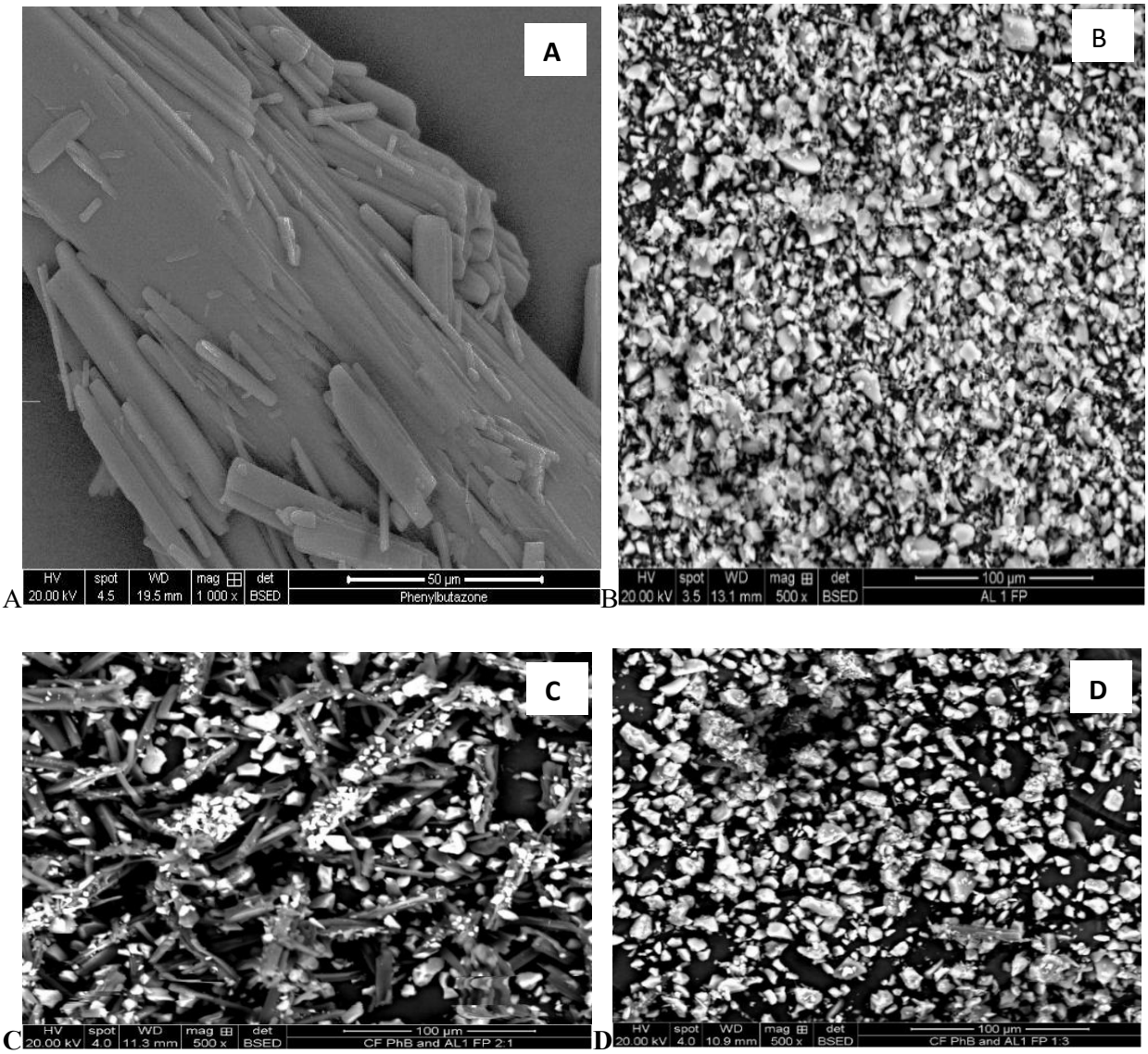

Figure 5: Scanning electron micrographs for particles of (A) phenylbutazone, (B) AL-1 FP (C) CF PhB and AL-1 FP 1:1 (D) CF PhB and AL-1 FP 2:1

As can be seen in Figure 6, crystalline phenylbutazone exhibited a well-defined sharp endothermic peak at 107^0C corresponding to its melting point. The characteristic peak of the drug appeared in the physical mixture at all drug/silica AL-1 FP ratio with little disparities for PhB/AL-1 FP 1:1 and 1:2 ratios in term of melting peak broadening and depression, providing an insight about solid state modifications and transition from crystalline to partially amorphous form of the drug.

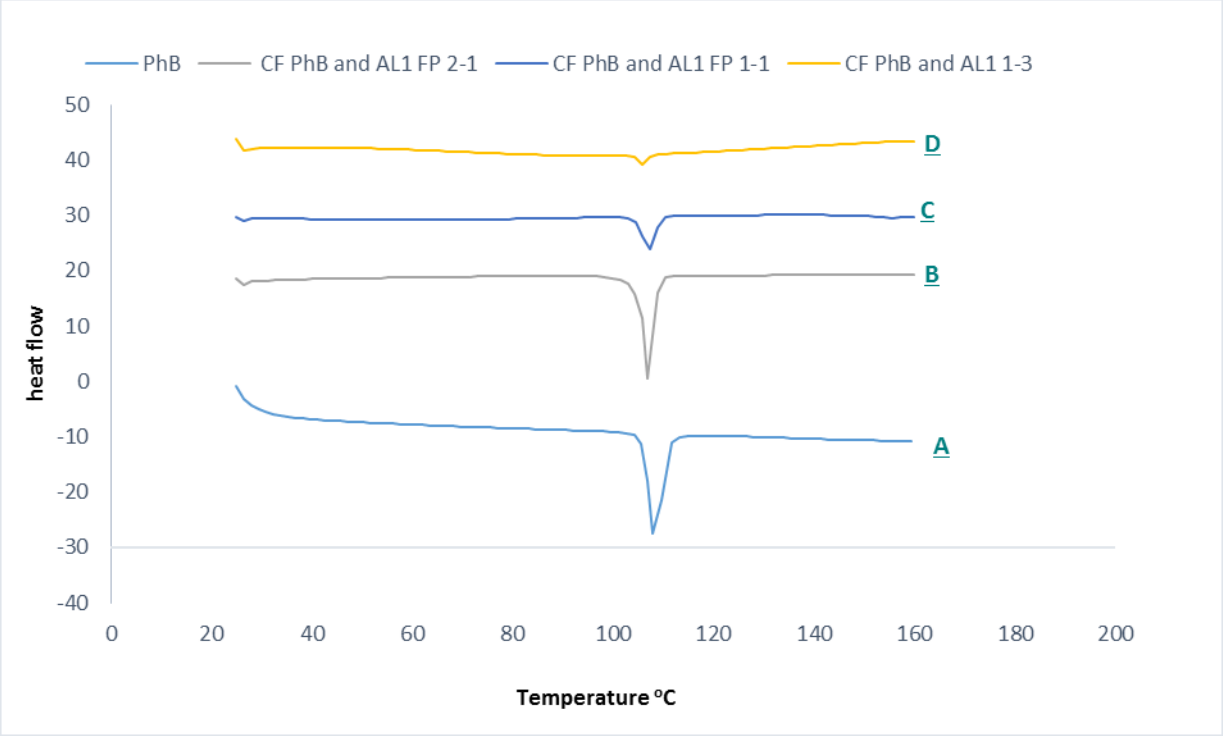

Figure 6: DSC profiles for phenylbutazone (PhB) along with AL-1 FP based physical mixture and conversional formulation (CF), (a) pure phenylbutazone (b) CF PhB and AL-1 FP 2:1 (C) CF PhB and AL-1 FP 1:1 (D) CF PhB and AL-1 FP 1:3

***In vitro* phenylbutazone release**

Dissolution profiles of phenylbutazone loaded Syloid silica's were investigated for a period of 45min in pH6.8 phosphate buffer. As can be seen in Figure 6, pure phenylbutazone that had not undergone the formulation process exhibited 12.3% (± 0.2%) drug release after 5min yet only increased to a maximum of 31.9% (± 3.9%) release after 45min. For many drugs, this low percentage of drug release after this time would be regard as unsuitably low and may limit bioavailability. Through undertaking the formulation process with the drug alone, i.e. hydration, heating, filtering, drying then sieving, the percentage of drug release, or more accurately in this case, dissolution after 45min was 31.9% (± 3.9%).

Therefore, it has been confirmed that exposure of the drug to the formulation process did not affect the profile observed, i.e. hydrating through sieving did not enhance the effects observed for phenylbutazone. All three CF PhB and AL-1 FP ratio-based formulations exhibited a dramatic enhancement in percentage dissolution, confirming that the presence of Syloid silica contributed to the increase. Firstly, CF PhB and AL-1 FP 1-1, ratio achieved a percentage release of 29.30% (± 3.6%) after only 5 min, i.e. almost nearest to that observed for drug alone, after a period of 45min, this value had increased to

74.5% (± 2.0%), far higher than that seen for drug alone or drug that had under gone the formulation process. Secondly, CF PhB and AL-1 FP 2:1 ratio show such a promising percentage release after 5 min 33.4% (± 4.9%) after a total of 45min the maximum percentage release increase to 71.4% (± 1.3%). Finally, CF PhB and AL-1 FP 1:3 ratios was found to be the most successful for enhancing percentage release with an impressive 68.5% (± 7.6%) released after 5 min, i.e. Greater than the total seen for pure drug after 45 min, increasing to a maximum of 98.9% (± 0.01%) release after 45 min. When determining why all three Syloid silica's enhanced the percentage of dissolution following a standard formulation method, it would appear that the transformation from the crystalline to amorphous form (as evidenced by XRD and dissolution profiles of processed samples) plays a key role.

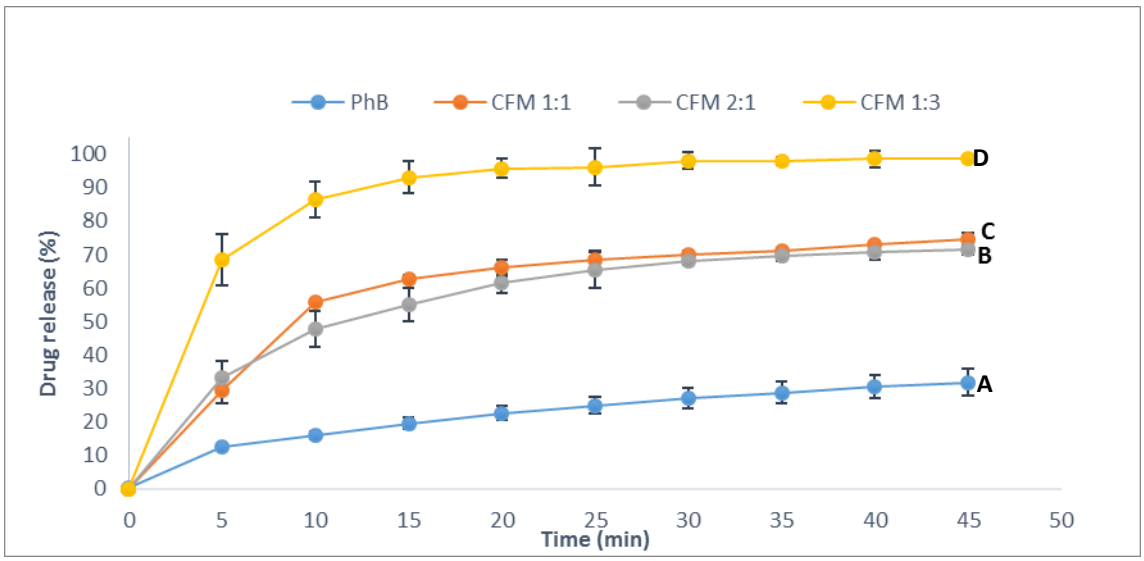

Figure 7. Phenylbutazone release profiles for phenylbutazone (PhB) processed phenylbutazone and Syloid silica AL-1 FP (1-1, 2-1, and 1-3) ratio. Each data point represents the mean of triplicate results (±SD).

Conclusion

In conclusion it has been confirmed that it is possible to formulate phenylbutazone with Syloid silica-based formulations to enhance the dissolution of a poorly soluble drug. Characterization data implies that this enhancement is a result of a change in crystallinity and the ability of the drug to enter pores within the Syloid silica structure. All three phenylbutazone with Syloid silica's (1:1,2:1,1:3) ratio analyzed demonstrated a dramatic increase in percentage release with their final percentage values linked to the Syloid silica pore diameter and/ or surface 67% increase. This finding can be of benefit for not only phenylbutazone-based

equine formulations but potentially a far wider range of compounds that exhibit it poor aqueous solubility, which will help all deviate bioavailability issues. To ensure that long-term stability is not constraint formulation development, it is will be a focus of future analysis, using techniques such as X-Ray Diffraction(XRD) and Scanning Electron Microscopy (SEM).

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