Insights Into *Parkia Biglobosa* Solid Dispersions Of Diclofenac Formulated By Kneading Method

Na'anman Charles Dagogot[1], Zwanden Sule Yahaya[2]*, Hassan Musa[1], Teryila Suzanne Allagh[1], Abdullahi Y. Idris[3]
[1]Department of Pharmaceutics and Industrial Pharmacy, Ahmadu Bello University, Zaria, Nigeria.
[2]Department of Pharmaceutics and Industrial Pharmacy, Kaduna State University, Kaduna, Nigeria.
[3]Department of Pharmaceutical and Medicinal Chemistry, Ahmadu Bello University, Zaria, Nigeria.
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***Corresponding author**: zwanden.yahaya@kasu.edu.ng; +234 80 60235790

ABSTRACT

Solid dispersion is widely utilized to promote the dissolution rate of molecules that are poorly aqueous soluble. This study aimed at enhancing the rate of dissolution and solubility of diclofenac sodium by utilizing solid dispersions prepared with *Parkia biglobosa* based - polymeric carriers. A phase solubility study was conducted to investigate the capacity of the polymers to improve the drug's solubility. Solid dispersions of *Parkia biglobosa* mucilage, modified *Parkia biglobosa* mucilage, and polyvinylpyrrolidone (PVP) at different drug to polymer ratios of 1:1, 1:2, and 1:3 were prepared by the kneading technique. The percentage yield, encapsulation efficiency, and solubility at pH 7.4 of the prepared solid dispersions were evaluated. Differential scanning calorimetry (DSC), X-ray diffraction, and Fourier transform infrared spectroscopy (FTIR) were used to characterize the formulations. The release rate of the encapsulated solid dispersions was also examined. At room temperature, the aqueous solubility of pure diclofenac sodium was found to be 18.64mg/ml. Diclofenac sodium solubility was increased by 1.8 and 2.6 folds with 0.5% *Parkia biglobosa* polymeric carrier and modified *Parkia biglobosa* polymeric carrier, respectively. The percentage yield ranged from about 66 to 97%. None of the formulations exhibited an encapsulation efficiency less than 75 %. The modified *Parkia biglobosa* polymeric based - solid dispersions all released over 95% of the drug within 30 minutes. The *Parkia biglobosa* polymeric based - solid dispersions prepared by the kneading method enhanced

the solubility and dissolution rate of diclofenac sodium.

Keywords: solid dispersion, diclofenac sodium, solubility, dissolution

INTRODUCTION

In modern pharmaceutics improvement in the dissolution rate and solubility of drugs that are poorly water-soluble is of great importance (Baird and Taylor, 2012). Bioavailability can be poor due to low water solubility or slow dissolution rates as in the case of drugs that belong to Biopharmaceutical Classification Systems (BCS) II, which are drugs with high permeability and low solubility. The bioavailability enhancement of BCS class II drugs can often be achieved by accelerating dissolution rates (Tekade and Yadav, 2020). Some approaches have been developed to improve the solubility and bioavailability of compounds with low water solubility, namely solid dispersion, lipid-based systems, complexation, nanonization, co-crystals, and micronization (Meng *et al.,* 2015; Yahaya *et al.,* 2017; Yahaya *et al.,* 2018). Among these, solid dispersion is among the most efficient and effective. A solid dispersion is a formulation that consists of a poorly water-soluble drug dispersed in at least one hydrophilic carrier, producing increased surface area, higher drug dissolution rate, and solubility (Hong, 2007; Huang and Dai, 2014; Na'anman *et al.,* 2017). Kneading, melting, solvent evaporation, and melting solvent techniques are all methods used to produce solid dispersion. Drug-hydrophilic carriers in solid dispersion can reduce agglomeration and release in a supersaturation environment, resulting in quick absorption and enhanced bioavailability. Other advantages of solid dispersion include promoting drug wettability and surface area, leading to increased drug aqueous solubility, the ability to produce a solid oral dosage form which is more convenient for patients than other forms like liquid products. Also, solid dispersion is void of disadvantages such as phase dissociation, increased hygroscopicity, and other stability issues inherent in other approaches such as salt formation (Tran *et al.,* 2019).

In preparing solid dispersion, many carriers are utilized, they could be surfactants (such as Inulin, Gelucire 44/14, poloxamer 407, etc), crystalline (e.g., urea, mannitol, etc), or polymeric carriers (Sheng *et al.,* 2018; Tran *et al*., 2019; Tekade and Yadav, 2020). The polymeric carriers can be natural or synthetic

polymers. Natural polymers include ethylcellulose, hydroxypropylmethylcellulose, or other starch derivatives and synthetic polymers include polyethylene glycol, povidone, and polymethacrylates (Tran *et al*., 2019; Tekade and Yadav, 2020). Polymers and other products derived from plants have gained tremendous interest in recent years due to their diverse pharmaceutical applications, ease of availability, sustainability, biocompatibility, biodegradability, non-toxic nature, bio-safety, and chemical inertness, making them preferable to synthetic ones (Yahaya *et al*., 2020a; Yahaya *et al.*, 2020b). As a result, demand for these compounds is increasing, and new sources are being discovered. In this work, diclofenac sodium solid dispersions were formulated using polymeric carriers derived from *Parkia biglobosa* seeds. The preparation, modification (carboxymethylation) and characterization of the *Parkia biglobosa* mucilage (PBM) and modified *Parkia biglobosa* mucilage (MPBM) has been previously reported (Dagogot *et al*., 2020). Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID) and a sparingly soluble phenylacetic acid derivative used to treat pain and inflammation in a variety of conditions (Sweetman, 2009). The aim of the study is to enhance the rate of dissolution and solubility of diclofenac sodium by utilizing solid dispersions prepared with polymeric carriers obtained from *Parkia biglobosa* seeds.

METHODS

Materials

Pal Pharmaceutical Limited in Kano, Nigeria, gave us diclofenac sodium as a gift. Sinopharm Chemical Reagent Co., Ltd. provided the polyvinylpyrrolidone. (China). The *Parkia biglobosa* mucilage and modified *Parkia biglobosa* mucilage were obtained from a batch processed in our laboratory. All other reagents used in the experiment were reagent-grade.

Phase Solubility studies

In each case, 100 mg quantity of diclofenac sodium powder was weighed and transferred into different 250 mL beakers each containing 5 of distilled water with varied (0%, 0.5%, 1.0%, 1.5%, 2.0% and 2.5%$^{w}/_{v}$) concentrations of PBM, MPBM and polyvinylpyrrolidone (PVP, as a standard). They were stirred for 45 minutes with a glass rod before being centrifuged at 1000 rpm for 15 min. A 0.45 µm Whatman filter paper was used to filter the supernatant, then the

concentration was determined spectrophotometically at 272 nm.

Preparation of solid dispersions and physical mixtures

Diclofenac sodium/carrier (i.e., PBM, MPBM, or PVP) in the ratios of 1:1, 1:2, and 1:3 were used to make the solid dispersion. In a mortar, the mixture was kneaded with a little amount of 50 % aqueous methanol solution. The kneaded mixture was transferred into a hot air oven until it reached a consistent weight. After complete drying, the resulting mixture was passed through a 250 µm mesh screen and kept in a screw cap vial in a desiccator at room temperature as K-PBM, K-MPBM, and K-PVP. By simply triturating the drugs and polymers in a mortar, physical mixtures (PM) of the drug and carriers with the same composition as the solid dispersions were prepared. The mixtures were sieved by passing through a 250 µm mesh sieve and stored in screw cap vials (as PM-PBM, PM-MPBM and PM-PVP) at room temperature in a desiccator for further assessment. The percentage yield of the physical mixture and the solid dispersion (SD) was calculated using Equation 1 (Noma *et al*., 2020).

$$\text{Percentage yield} = \frac{\text{The final weight of the SD or PM}}{\text{Initial Weight of Drug+Initial Weight of Polymer}} \text{X } 100 \quad \ldots 1$$

Encapsulation efficiency determination

Weighed solid dispersion (K-PBM, K-MPBM, and K-PVP) and physical mixtures (PM-PBM, PM-MPBM and PM-PVP) containing 10 mg diclofenac sodium was transferred to a 250 mL volumetric flask containing 100 mL phosphate buffer pH 7.4 and stirred for 15 min with a magnetic stirrer. A 1 mL sample was measured, diluted and spectrophotometric analysis (at 272 nm) was used to determine its concentration. Equation 2 was used to calculate the amount osf drug encapsulated in the solid dispersion (Musa *et al*., 2011).

$$\% \text{ Drug content} = \frac{\text{Actual SD drug content}}{\text{Theoretical SD drug content}} \ldots 2$$

Solubility determination in simulated intestinal fluid (pH 7.4)

The equivalent of 100 mg of diclofenac sodium from the solid dispersions and physical mixtures was weighed and

transferred to a 100ml beaker containing 5 ml of Simulated Intestinal Fluid (SIF) pH 7.4. The sample was stirred for 45 minutes with a glass rod before centrifugation at 1000 rpm for 15 min. A 0.45 µm Whatman filter paper was used to filter the supernatant solution. Then, a 1 mL sample was measured, diluted, and the amount of diclofenac sodium was spectrophotometrically determined at 272 nm.

***In vitro* drug release study**

The pure drug, physical mixtures (PM-PBM, PM-MPBM and PM-PVP), and solid dispersions (K-PBM, K-MPBM, and K-PVP) equivalent to 100 mg of diclofenac sodium were encapsulated (filled into a size '0' hard gelatin capsule) and placed in the dissolution basket of the Erweka dissolution apparatus. The experiment was conducted in 900 ml of phosphate buffer (pH 7.4) maintained at 37 $\pm$ 0.5 ^{o}C and 50 rpm. At intervals of 10 to 60 minutes, 2mL of the dissolving media was withdrawn and replaced with a fresh medium of equal volume. A 0.45 µm Whatman filter paper was used to filter the withdrawn sample, which was then diluted and its absorbance at 272 nm was measured spectrophotometrically to determine the drug content and percentage release.

Interaction studies on the solid dispersions

Fourier transform infrared (FT-IR)

The FTIR spectra of the pure drug and the different solid dispersions (K-PBM, K-MPBM, and K-PVP) were obtained using an FT-IR spectrophotometer (Aligent technologies Cary 630) across the range 500 - 4500 cm^{-1} to analyze probable interactions between diclofenac sodium and the different polymers employed.

Differential scanning calorimetry (DSC)

The pure drug and solid dispersions (K-PBM, K-MPBM, and K-PVP) were evaluated using DSC (DSC3 Mettler Toledo) by heating the samples at a rate of 10 ^{O}C per min and a temperature range of 30 to 300 ^{O}C to identify the probability of interaction.

X-ray powder diffraction (XRPD) studies

To assess the powder's properties, X-ray diffraction patterns of diclofenac sodium, physical mixtures (PM-PBM, PM-MPBM and PM-PVP), and solid dispersions (K-PBM, K-MPBM, and K-PVP) were recorded using the diffractometer (Brukar AXS DH Advance, Germany). The scanning rate used was 6^{0} min^{-1} over the 10 to 50^{0} diffraction angle (2θ) range.

Statistical analysis

The obtained data were expressed in the form of mean ± standard deviation (SD). Using

SPSS 23 software (SPSS, Chicago, IL, USA), data were analyzed using a one-way analysis of variance (ANOVA) followed by the Bonferroni *post hoc* test for multiple comparisons. At $p < 0.05$, the results were considered significant.

RESULTS

At room temperature (28 ± 2°C), the aqueous solubility of pure diclofenac sodium was found to be 18.64mg/ml. The phase solubility diagram shows a linear relationship between increased diclofenac sodium solubility and the increasing concentration of the three distinct polymers (PBM, MPBM, and PVP). The polymers improved diclofenac sodium aqueous solubility in the following order: PVP>MPBM>PBM. Figure 1 shows the phase solubility diagram.

The percentage yield, encapsulation efficiency and results of solubility studies of the different diclofenac sodium solid dispersions and physical mixtures are shown in Table 1. The percentage yield ranged from about 66 to 97%. None of the formulations exhibited an encapsulation efficiency less than 75 %. All the solid dispersions and physical mixtures achieved significant (p = 0.000) improvements in the diclofenac sodium apparent aqueous solubility.

The dissolution profiles of the free diclofenac sodium and solid dispersions in SIF (pH 7.5) are presented in Figures 2, 3 and 4. All the solid dispersions exhibited faster drug release than the free diclofenac sodium powder.

The FTIR spectrum of diclofenac sodium showed characteristics N-H stretching at 3257.19 cm^{-1}, -C=C aromatic stretch at 1568.73 cm^{-1} and 1502.11 cm^{-1} C-N at 1450 cm^{-1}, -C-Cl at 1091.81 cm^{-1}, and 743.38 cm^{-1} for meta substituted benzene. These bands are all retained in the IR spectra of K-PBM, K-MPBM and K-PVP as shown in Figure 5.

The DSC thermogram of diclofenac sodium showed an exothermic event at between 35 ^{O}C to 40 ^{O}C indicatives of its melting peak which is retained in the thermograms of the solid dispersions. The DSC thermograms of diclofenac sodium, K-PBM, K-MPBM and K-PVP are presented in Figure 6.

The XRPD patterns of diclofenac sodium, K-PBM, K-MPBM and K-PVP as shown in Figure 7. The diffractogram of diclofenac sodium showed several sharp peaks within the range of 10-35 0 Ɵ. The intensity of these peaks is reduced in the diffractogram of the physical mixtures and disappeared in the

diffractogram of the solid dispersions of the diclofenac sodium.

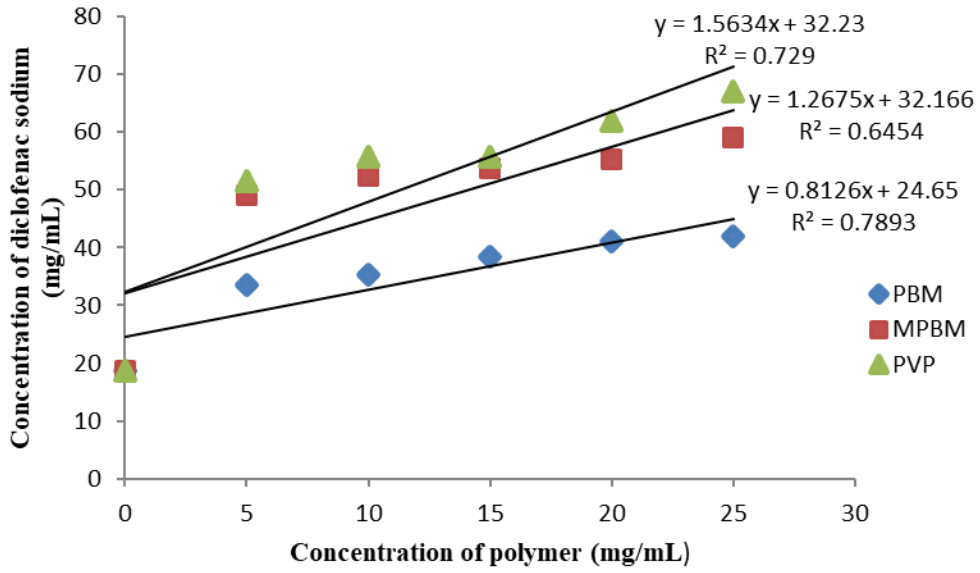

Figure 1: Phase solubility diagram of diclofenac sodium with PBM, MPBM and PVP

Table 1: Percentage yield, encapsulation efficiency and solubility measurements of solid dispersions and physical mixtures (±SD)

		Ratios		
Test	**Formulation**	1:1	1:2	1:3
Percentage yield	K-PBM	76.50±2.12	86.15±0.21	89.10±0.14
	K-MPBM	85.00±0.00	88.68±0.03	92.75±0.40
	K-PVP	66.50±0.71	77.38±0.64	82.55±0.07
	PM-PBM	94.10±0.14	97.39±0.08	97.44±0.08
	PM-MPBM	93.00±0.00	95.36±0.05	96.53±0.04
	PM-PVP	87.28±0.40	93.27±0.09	92.54±0.05
Encapsulation efficiency (%)	K-PBM	88.26±1.22	86.40±0.00	77.06±0.46
	K-MPBM	89.60±1.38	78.13±0.46	78.67±0.46
	K-PVP	86.67±1.22	89.60±0.00	84.00±0.00
	PM-PBM	80.93±0.58	81.87±6.80	75.73±0.46
	PM-MPBM	80.0±0.00	78.13±0.46	84.26±0.46
	PM-PVP	81.87±0.46	77.87±3.95	78.67±1.22
Solubility (mg/mL)	K-PBM	60.60±0.28	61.00±0.28	74.00±0.00
	K-MPBM	66.00±1.13	88.70±0.70	89.40±0.85
	K-PVP	79.20±0.00	91.00±0.28	93.20±0.00
	PM-PBM	34.00±0.00	34.80±0.00	34.80±0.00
	PM-MPBM	57.20±0.57	59.20±2.82	62.80±1.13
	PM-PVP	48.21±0.00	56.80±0.57	63.60±0.00

All solid dispersions and physical mixtures exhibited significantly (p = 0.000) higher solubility than diclofenac sodium (18.64mg/ml at 28 ± 2°C).

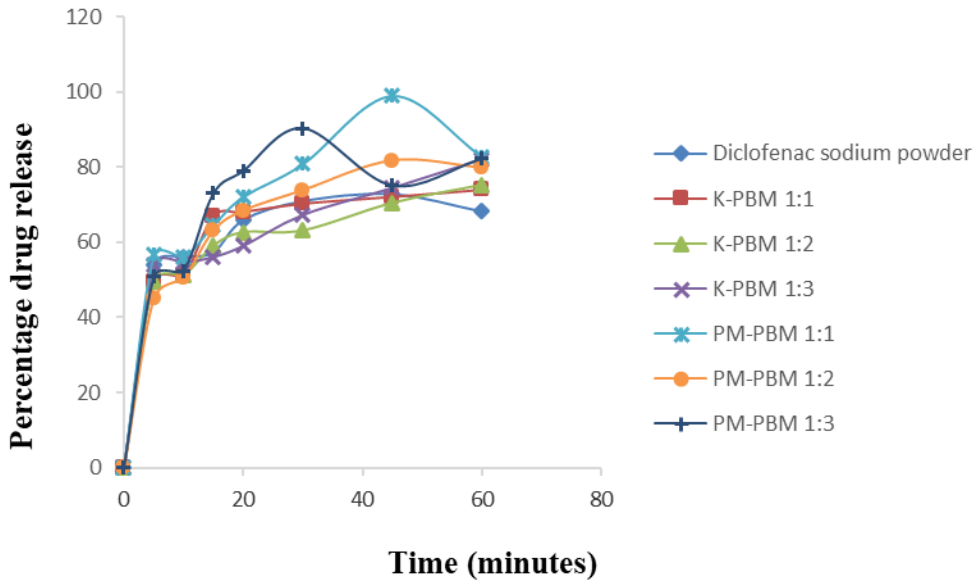

Figure 2: Percent drug released from diclofenac sodium powder, K-PBM 1:1, K-PBM 1:2, K-PBM 1:3, PM-PBM 1:1, PM-PBM 1:2 and PM-PBM 1:3

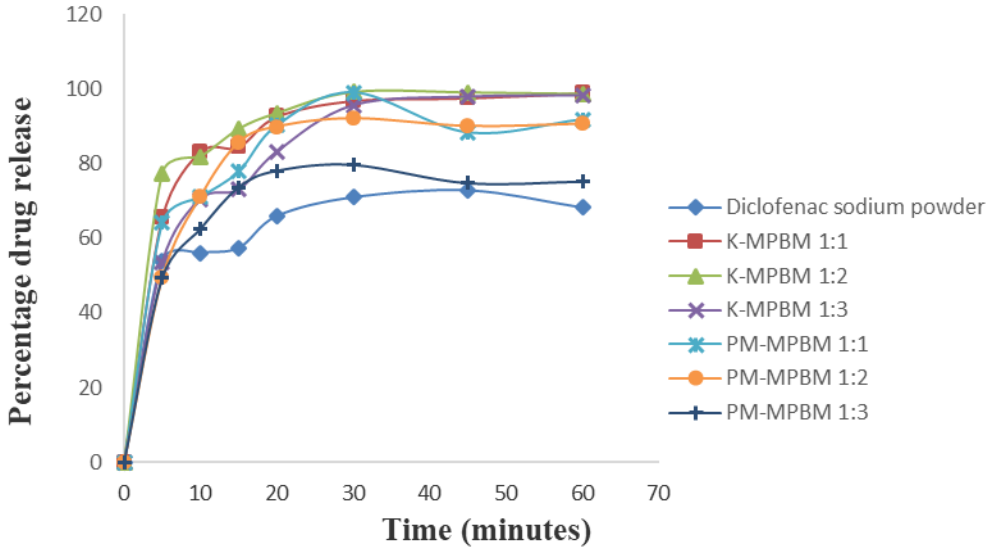

Figure 3: Percent drug released from diclofenac sodium powder, K-MPBM 1:1, K-MPBM 1:2, K-MPBM 1:3, PM-MPBM 1:1, PM-MPBM 1:2 and PM-MPBM 1:3

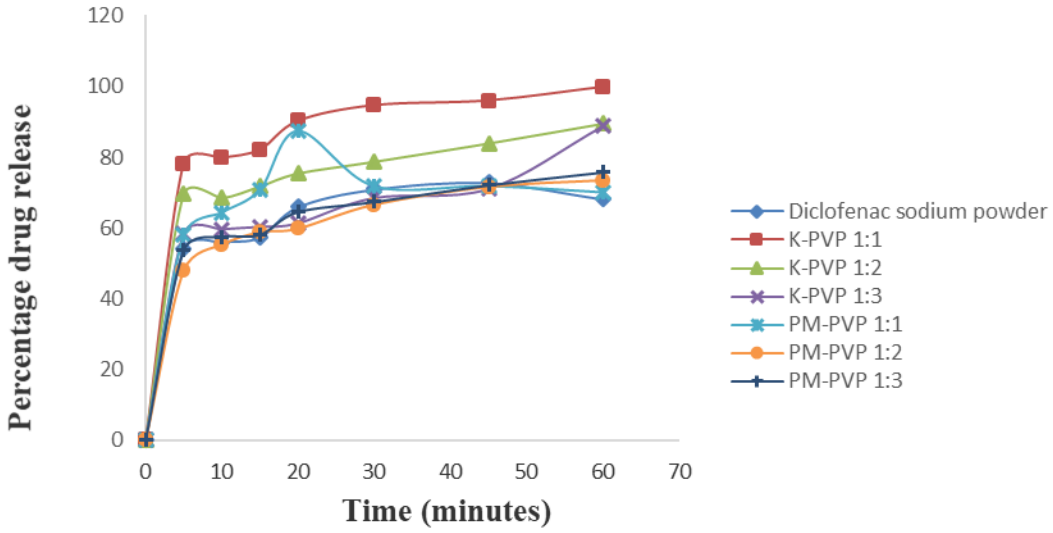

Figure 4: Percent drug released from diclofenac sodium powder, K-PVP 1:1, K-PVP 1:2, K-PVP 1:3, PM-PVP 1:1, PM-PVP 1:2 and PM-PVP 1:3

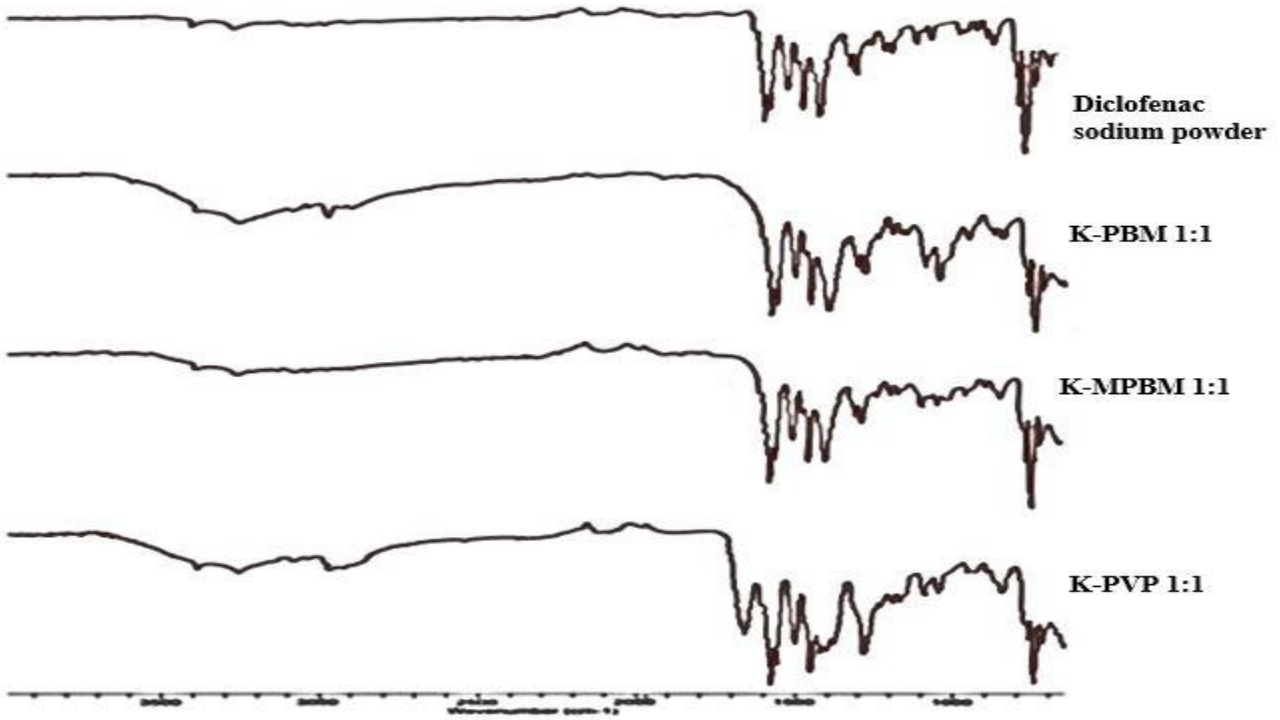

Figure 5: The FTIR spectra of diclofenac sodium powder, K-PBM 1:1, K-MPBM 1:1 and PVP-1:1

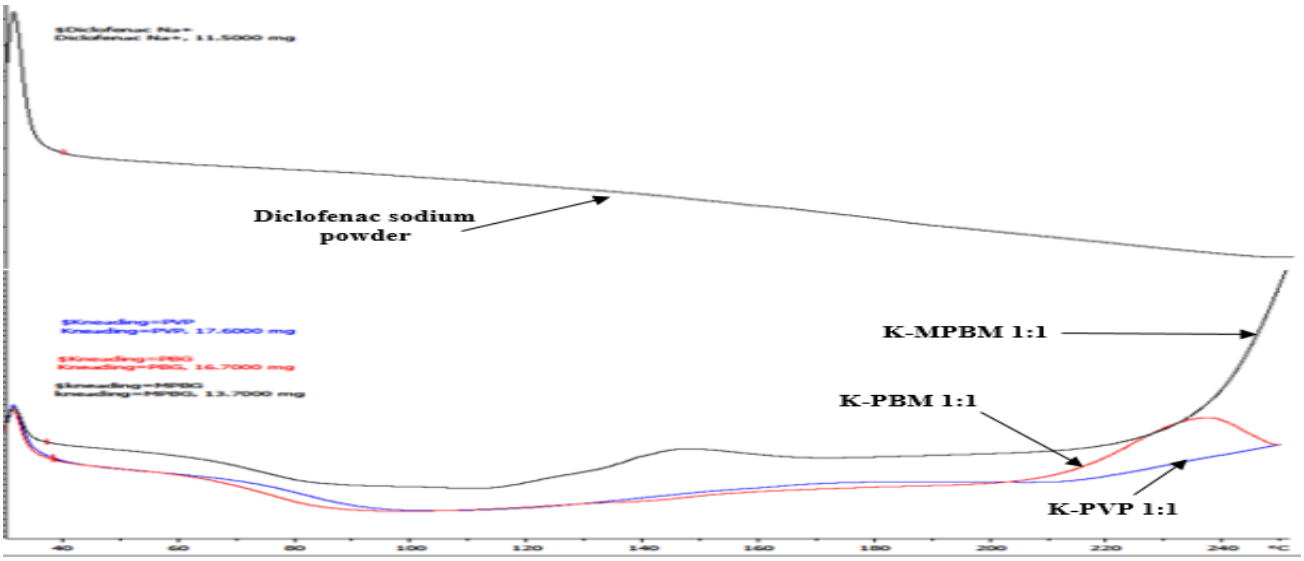

Figure 6: The DSC thermograms of diclofenac sodium powder, K-PBM 1:1, K-MPBM 1:1 and PVP-1:1

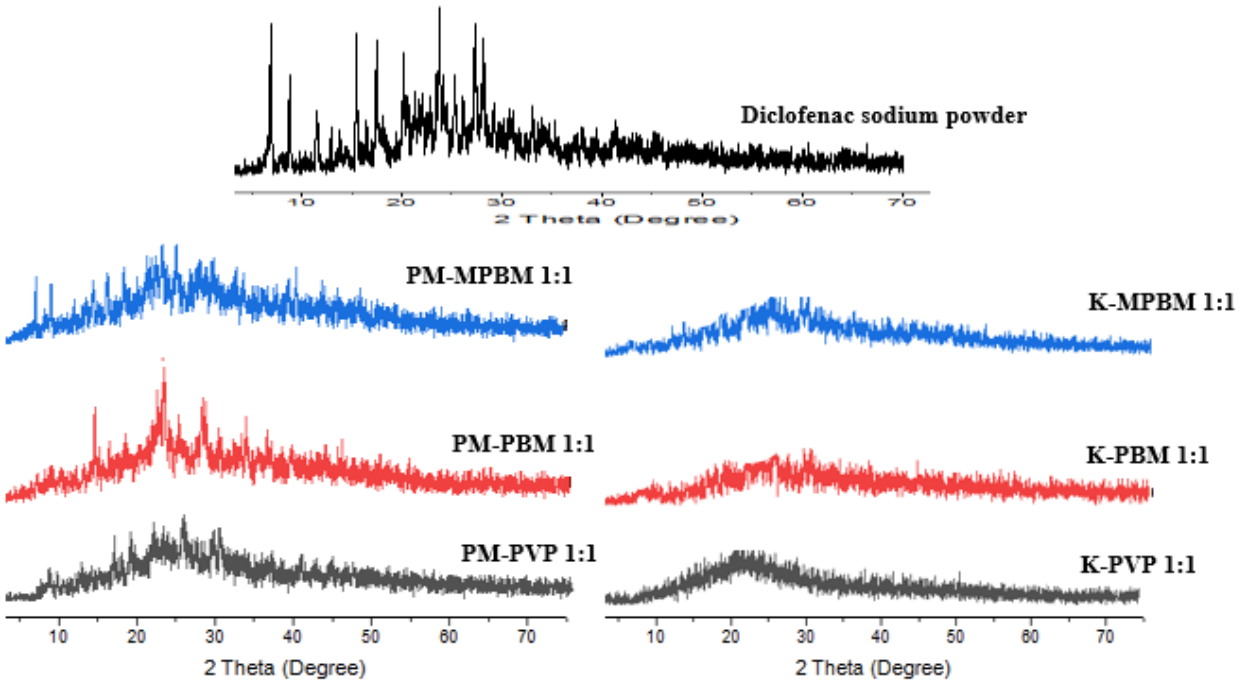

Figure 7: The x-ray diffraction patterns of diclofenac sodium powder, PM-MPBM 1:1, PM-PBM 1:1, PM-PVP, 1:1K-PBM 1:1, K-MPBM 1:1 and PVP-1:1

DISCUSSION

According to phase solubility studies, the solubility of diclofenac sodium increased by 1.8 and 2.6 folds with 0.5 % PBM and MPBM, respectively, and by 2.3 and 3.2 folds with 2.5 % PBM and MPBM. This demonstrated that PBM and MPBM could both effectively increase the solubility of diclofenac sodium at lower concentrations. The wettability action of the polymers could be responsible for the observed increase in diclofenac sodium solubility (Fael *et al*., 2018). The improvement in solubility was higher with MPBM as compared to PBM, this is not unconnected to the higher hydrophilicity of MPBM as reported in our previous finding (Dagogot *et al*., 2020).

Improved polymer ratio provides for better management of the unit processes involved in the formation of solid dispersions, which could explain the increased yield seen as the polymer ratio rises. Encapsulation efficiency refers to the consistency of the content, the measure to which the drug is incorporated into the solid dispersion, and the adequacy of the technique used to make the solid dispersions. None of the formulations had less than a 75% encapsulation efficiency. This could be attributable to the effectiveness

of the kneading technique as a procedure for preparing solid dispersions; a similar perspective was shared by Sarangi and Sigh, (2018).

All the bands shown by diclofenac sodium are retained in the IR spectra of the solid dispersions. Liang et al., (2015) found that solid dispersion of diclofenac with ethyl cellulose and PEG 2000 retained similar peak position and intensity, and attributed this to the absence of drug-polymer chemical interaction. This suggests that the components of the formulation are compatible (Yahaya *et al*., 2020a). This is further supported by the retention of the exothermic peak observed in the DSC thermograms of the solid dispersions. However, a reduction in peak intensity was noticed in the DSC thermograms of the solid dispersions, which was attributable to molecular dispersion or solubilization of the drug in the molten polymer to generate eutectic mixtures, according to findings in the literature (Na'anman *et al.*, 2017; Tambe and Pandita, 2018). The diclofenac sodium diffraction pattern has a high degree of crystallinity, as evidenced by the high peaks. In contrast, the kneading process resulted in fully amorphous solid dispersions with lost crystallinity, as evidenced by the absence of peaks in the solid dispersions' x-ray diffractograms. It has been suggested that the loss of x-ray diffractogram peaks in a drug molecule is due to the drug's transition from crystalline to amorphous form (Borba *et al*., 2016).

When compared to the free drug, the solid dispersions of PBM increased by 3.3 and 4 folds for 1:1 and 1:3, respectively, while those of MPBM increased by 3.5 and 4.8 folds for 1:1 and 1:3. K-PBM 1:3 and K-PVP 1:3 (the standard polymer) had similar solubility enhancement. When compared to the free drug, the physical mixtures PM-PBM 1:3 and PM-MPBM 1:3 showed a 1.9 and 3.4-fold increase in solubility, indicating that using PBM and MPBM as carriers can increase diclofenac sodium solubility This could be due to the carriers' hydrophilic structures. Because of the polymers' combined surface activity, wetting, and solubilization effect, the polymer particles may have hydrated quickly to form a polymer solution, which dissolved the adjacent drug particles. These values, on the other hand, are much lower than those of solid dispersions, indicating that the higher solubility of solid dispersions is closely linked to the molecular dispersion of the drug into the carrier and system in an amorphous solid dispersion. As

a result, the drug's solid-state properties are the only reason for the differences in solubility or full amorphization. Amorphous compounds have a more disordered molecular arrangement than crystalline compounds, and such disorder is the main driver behind their faster dissolution rates and higher solubility. Furthermore, the amorphous state frequently has the advantage of reduced particle size and improved wettability, which may enhance solubility (Borba *et al.*, 2016).

The dissolution rate of a drug in the GI tract usually limits the rate of oral absorption. A drug substance's dissolution rate is highly dependent on physical properties such as amorphism, polymorphism, crystallinity, whether it is a solvate or hydrate, the surface area and particle size (Fael *et al.*, 2018). The dissolution profile of the crystalline plain drug was the worst, whereas the dissolution rate of the amorphous solid dispersions was dramatically improved. This was to be expected, because, as previously stated, the dissolution process is highly dependent on a compound's physical properties. Solid dispersions prepared with MPBM had the highest release rates, with all of them exhibiting higher and faster release than those prepared with the standard polymer (PVP). Within 30 minutes, they (K-MPBM 1:1, K-MPBM 1:2, and K-MPBM 1:3) all released over 95% of the drug. The instantaneous fast release could be attributed to the solid-state of diclofenac sodium in the solid dispersion, which was mostly amorphous, as well as the combined action of surface activity, solubilisation, and wetting effect of the hydrophilic polymers. In a few instances, some physical mixtures (PM-PBM 1:1 and 1:3) exhibited better dissolution rates than the solid dispersions. Solid dispersion particles may dissolve slowly due to the nature of the polymer, resulting in a more sustained release profile (Huang and Dai, 2014). PBM exhibited higher viscosity in aqueous media than the MPBM as previously reported (Dagogot *et al*., 2020). The formation of a highly viscous gel upon contact with the dissolution medium may have slowed the release rates of the molecularly dispersed drug when compared to the physical mixture, which is a simple dispersion of drug in the polymer.

CONCLUSION

The solid dispersions of polymeric carriers obtained from *Parkia biglobosa* seeds with diclofenac sodium were studied using phase solubility, DSC, FTIR, XRPD, saturation solubility, and *in vitro* drug release and

compared to solid dispersions of a commonly used polymer, PVP. The FTIR and DSC analysis revealed that the polymers had no interaction with the drug. The x-ray diffractogram underwent a transformation from crystalline to amorphous, which may be responsible for the drug's increased solubility and dissolution rates. The solid dispersion technique used is thus a simple, easy, and reproducible method that could prove to be a cost-effective and beneficial approach to improving diclofenac sodium aqueous solubility and drug release performance, potentially aiding in improving oral bioavailability.

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Conflicts interests

The authors declare no conflict of interest.

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