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Preparation And Evaluation of Naproxen Ternary Solid Dispersion Using Genetically Modified Cassava Starch and Hydroxypropyl Methyl Cellulose

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Naproxen has poor aqueous solubility and high permeability, making its formulation into oral dosage form challenging. The objective of this work was to enhance naproxen aqueous solubility by formulating it into solid dispersion (SD) using genetically modified cassava starch (GMCS) and hydroxypropyl methyl cellulose (HPMC) as polymers, and polysorbate-80 as surfactant.

Materials and Methods: Naproxen SD was prepared by solvent evaporation. Different polymer-drug ratios (1:1, 2:1, 3:1 and 4:1) were used. The SDs were evaluated for solubility and the optimum formulation (S2) subjected to Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC) and scanning electron microscopy (SEM). Pure naproxen tablets (TN) and S2 tablets (T2) were directly compressed and assessed for hardness, friability, weight uniformity, disintegration and dissolution times.

Results: The SD of polymer/drug ratio 2:1 and GMCS/HPMC proportion 2:1 had the highest solubility with the polymers showing synergism. Incorporating polysorbate-80 improved solubility by over 20 folds. SEM micrograph of the SD appeared smooth and spherical. DSC thermogram indicated a reduction in crystallinity of naproxen. FTIR spectrum showed no evidence of interaction with the polymers. T2 and TN tablets showed acceptable hardness, disintegration time and weight uniformity. The t_{50} and t_{90} dissolution values for T2 were 4.9 and 37.7 minutes respectively which were considerably lower than that of TN (28.57 and 63.42 minutes).

Conclusion: Naproxen solubility was enhanced by solid dispersion formulation using genetically-modified cassava starch/HPMC blend. Synergistic effect in the improvement of naproxen solubility was established between the polymers. Inclusion of polysorbate-80 also improved naproxen solubility in the solid dispersion.

Keywords: Aqueous solubility, Naproxen, Cassava starch, Solid dispersion.

INTRODUCTION

The aqueous solubility of orally administered drugs is essential to their bioavailability. One of the most important factors in attaining optimal drug concentrations in systemic circulation to demonstrate pharmacological response is the drug's solubility. Biopharmaceutical classification system (BCS) classes II and IV drugs are poorly absorbed because of their low aqueous solubilities.

Efforts at improving the solubility of drugs such as nanoparticle delivery (Wilczewska *et al.*, 2012), salt formation (Serajuddin, 2007) and cyclodextrin complexation (Challa *et al.*, 2005) are with attendant limitations. Solid dispersion involves the enhancement of the solubility of poorly soluble drugs and the dispersion of one or more active agents in a matrix in a solid state (Alshehri *et al*., 2020). The high rate of solubility and dissolution exhibited by amorphous solid dispersion is due to the existence of the drug in a high energy amorphous state. Also, the inclusion of surfactants, such as polysorbate 80 in solid dispersion formulations further increases solubility and dissolution rate by increasing wettability or causing the formation of micelles (Nair *et al.*, 2020).

Synthetic polymers are amenable to modification due to their strong mechanical strength and have been used as carriers in solid dispersion formulations (Ghosh, 2004; Ueda *et al*., 2018). The polymers are however less biocompatible and can elicit inflammation and low clearance from the plasma (Lee & Shin, 2007). The use of natural polymers is being encouraged because of their safety, biodegradability and renewability (Bealer *et al.*, 2019).

Starch, the second most abundant polysaccharide, has found extensive use in the pharmaceutical field due to its non-toxicity, biodegradability and biocompatibility. These, in addition to its hydrophilic nature, are responsible for its acceptability (Maniglia *et al.*, 2021). Starch, like other natural polysaccharides, however, is limited by poor mechanical strength which makes its processing difficult. To improve on these limitations, starch is often modified or blended with other polymers.

Hydroxypropyl methyl cellulose (HPMC) is a semi-synthetic derivative of the natural polymer, cellulose. It has been widely used in food and drug industries as a stabilizer, binder, coating agent and film former (Burdock, 2007). HPMC is hydrophilic and has been shown to enhance the properties of starch when blended (Ayorinde *et al.*, 2016).

Naproxen is a 2-aryl propionic non-steroidal anti-inflammatory drug. The drug belongs to class II of the BCS and its bioavailability is therefore limited by poor aqueous solubility. This work was aimed at using genetically modified cassava starch (GMCS) and HPMC as matrix for naproxen solid dispersion. The effect of polysorbate 80 on the solubility of the solid dispersion was also evaluated.

METHODOLOGY

Material and Methods

Material

Naproxen (BOC sciences, London), genetically modified cassava starch (IITA, Ibadan), HPMC (Zhejiang Haishen Chemical Co. Ltd, China), Ethanol (Merck, Germany), Polysorbate 80 (Sigma-Aldrich Chemie GmbH, Germany). All other reagents are of analytical grade.

Methods

Starch Extraction

Starch was extracted by the method described by Ayorinde *et al.* (2016). Genetically modified cassava tubers were washed, peeled and chopped into smaller pieces and were later blended using a laboratory blender. Excess water was added to the slurry and a muslin cloth was used for filtration. The filtrate was kept for 24 hours and the supernatant decanted. The sediment was washed daily over 84 hours. The collected residue was allowed to dry at 50°C for 2 days in an oven. The dried mass was powdered and stored in an airtight container.

Characterization of starch

Bulk and tapped densities

The starch sample (30 g) was weighed and the quantity poured into a 100 mL measuring cylinder. The volume occupied by the starch was recorded as the bulk volume. The container was subjected to 100 taps at 38 taps per minute. The volume of the starch after tapping was denoted as the tapped volume. The corresponding tapped and bulk densities were estimated thus;

$$bulk\ density = \frac{weight\ of\ starch}{bulk\ volume}$$

$$tapped\ density = \frac{weight\ of\ starch}{tapped\ volume}$$

Hausner's ratio (HR) and Carr's index (CI)

These were estimated using the following relationships;

$$HR = \frac{tapped\ density}{bulk\ density}$$

$$CI = \frac{tapped\ density - bulk\ density}{tapped\ density}\ x\ 100$$

Angle of repose

This was determined using a modification of the method described by Iwuagwu and Onyekwelli (2002). A funnel was fixed 2cm above a horizontally placed graph paper. 20g of starch was passed through the funnel until a formed heap was touching the tip. The heap height and the mean diameter of the base were determined and the angle of repose was calculated using the formula;

$$tan\theta = \frac{height}{radius}$$

Swelling index

The swelling index was calculated by placing 10 g of the genetically modified cassava starch in a 100ml-measuring cylinder and measuring the tapped volume, Vt. Water was added up to the 70ml mark and the cylinder was shaken for a few minutes. The volume was made up to 100ml and the cylinder was kept at room temperature for 24 hours. The sedimentation volume, Vs, after 24 hours was noted.

$$\text{Swelling index} = \frac{Vs}{Vt}$$

Determination of pH

A 1% suspension of the genetically modified cassava starch was prepared and the pH value was measured using a pH meter (F-21 Horiba, Japan).

Water absorption capacity

The genetically modified cassava starch (1g) was dispersed in 10mls of water in a centrifuge tube and the mixture stirred and left for 4 hours. The tube was subjected to centrifugation at 3500rpm for 30 minutes. The supernatant was measured and the difference between 10ml and the volume of the supernatant was noted as the amount of water absorbed.

Preparation of naproxen solid dispersion

The solid dispersion preparations were made by the solvent evaporation technique. The formula for the preparation are shown in Table 1. In each case, the polymer or polymer blend of appropriate ratios is added to a premixed solution of 0.5g polysorbate 80 in 80% ethanol. Naproxen (2g) was then placed in the solution and the mixture was stirred on a magnetic stirrer to get a slurry. The slurry was air dried and the resulting solid mass was pulverized. The powder was passed through a size 60 mesh, kept in an airtight container and labelled.

Table 1: Solid dispersion formulations

Formulation	S1	S2	S3	S4	S5	S6	S7	S8
Naproxen (g)	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
GMCS (g)	1.33	2.67	6.00	2.00	4.00	8.00	--	1.33
HPMC (g)	0.67	1.33	--	--	--	--	2.00	0.67
Polysorbate 80 (g)	0.50	0.50	0.50	0.50	0.50	0.50	0.50	--
Polymer/drug ratio	1:1	2:1	3:1	1:1	2:1	4:1	1:1	1:1

GMCS = genetically modified cassava starch, HPMC = hydroxypropyl methyl cellulose

Solubility of Solid Dispersion

50mg of solid dispersion samples were each weighed and added to 50ml distilled water in a beaker. The content was subjected to continuous magnetic stirring for 5 hours. The resulting liquid was filtered and the absorbance observed at 480nm using a UV-Vis spectrophotometer (PG Instruments Limited, UK). The solid dispersion with the highest naproxen solubility was noted and solid dispersion tablets were made therefrom. The process was repeated for the pure naproxen.

Preparation of solid dispersion tablet

A quantity of solid dispersion containing 100mg of naproxen was mixed with respective quantities of magnesium stearate, calcium carbonate and corn starch, as shown in Table 2. Tablets were made by direct compression at a compression force of 1 metric ton and 30 seconds dwell time, using a single punch hydraulic tabletting press (Model 38510E Carver Inc. USA). The tablets were stored for further analysis.

Table 2: Formulation table for solid dispersion and pure naproxen tablet

Formulation Code	Equivalent SD of 0.1g naproxen (g)	Magnesium Stearate (g)	Cornstarch (g)	Calcium Carbonate (g)
T2	0.30	0.05	0.05	0.1
TN	0.10	0.05	0.05	0.3

T2 = Tablet of solid dispersion S2, TN = tablet of pure naproxen

Characterization of solid dispersion and tablets

Fourier-transform infrared spectroscopy

The FTIR spectra of pure naproxen, genetically modified cassava starch, HPMC and the solid dispersion powder were generated with an FTIR spectrophotometer (Agilent Cary 630 FTIR). Potassium bromide (KBr) disk was prepared by a mixture of the solid dispersion powder and KBr and the scan was run between 600 cm^{-1} and 4000 cm^{-1}.

Differential scanning calorimetry

The DSC thermograms were generated on a differential calorimeter with the aid of a thermal analyzer (Mettler Toledo DSC 2). Approximately 2mg of the powder was weighed and placed in a sealed aluminium pan under nitrogen flow. It was then heated at a scanning rate of 5°C/min. An empty aluminium pan was used as standard.

Scanning electron microscopy

The granular shape of pure naproxen, genetically modified cassava starch, HPMC, and the solid dispersion powder was observed with a scanning electron microscope (JEOL JSM 7600F. The powdered mixtures were rigidly fixed on the specimen stub and were coated with platinum coating of electrically conducting material deposited in a vacuum using Hitachi Ion Sputter (E-1030) for 240 seconds at 15mA.

Weight variation of tablets

Five tablets from each batch of tablets were randomly picked and the weight determined using an analytical balance. Average weight was obtained for each batch. Each tablet was separately weighed and the percentage deviation from the average weight was recorded.

Tablet hardness

With the aid of a hardness tester (Ketan, India), the diametral compression method was used to gauge the tablets' hardness. Values for each batch were recorded in triplicate, and the mean values were determined.

Tablet friability

A friability tester (Shivani Scientific, India) was used to conduct the test. The apparatus was filled with ten (10) previously weighed tablets (W1). These were then subjected to rolling and repeated shocks as they fell in each rotation. The tablets were weighed (W2) after 4 minutes of treatment, or 100 rotations, and the percentage friability (F) was determined using the formula:

$$F = \frac{(W_1 - W_2)}{W_1} \times 100$$

Tablet disintegration test

The disintegration test was carried out using Veego tablet disintegration apparatus (India). The apparatus consists of cylindrical baskets woven into metal held by a motor shaft, beakers and a heater. The beakers and disintegration medium (distilled water) were allowed to warm to 37˚C. The tablets were randomly picked and put in each basket. A stopwatch was used to note how long it took each tablet to completely disintegrate and pass through the basket.

Drug release

The dissolution test was done with a USP Dissolution apparatus II. Each tablet sample containing 100mg of naproxen was added to 900mL of the dissolution medium (pH 7.2) at 37±0.5°C and 100 rpm. At scheduled times, 5ml of the medium was removed and filtered, and the absorbance examined with a UV-visible spectrophotometer (PG Instruments, UK) at a wavelength of 480nm. Each time, the withdrawn 5ml samples were replaced by same amount of the medium.

Statistical Analysis

Statistical analysis of data was carried out with GraphPad Prism® 10 using Student's t-test and ANOVA, and taking $p<0.05$ as the limit of significance (GraphPad Software Inc. San Diego, USA).

RESULTS AND DISCUSSION

Physicochemical properties of starch

The genetically modified cassava starch was characterized and the results are shown in Table 3. The Hausner's ratio and Carr's index of GMCS were respectively 1.22 and 18.1%. These two parameters are used to assess the flowability of powders. The value of Carr's index indicated that the starch had a fair flow but a better compressibility. Powders with Carr's index values below 15 and above 25 are considered good flowing and poor flowing respectively. The GMCS therefore possessed a fair flow based on its Carr's index value. The Hausner's ratio of 1.22 also showed that the starch possessed a fair flow. The angle of repose of the starch was calculated to be 39.1% which is a further indication of the fair flowability of the starch. The flow properties of starches are determined by the size, shape and the tendency of the granules to stick together (Bhatt *et al.*, 2023). The particles of GMCS are polygonal in shape which could have contributed to the enhancement of flow of the granules. Lawal *et al*. (2015) determined Carr's index and Hausner's ratio for native cassava starch to be 40 and 1.67 respectively. The flow properties were reported to improve with modification of the starch by acetylation and pre-gelatinization. The values recorded for the flow parameters in this work showed that GMCS had better flowability than native cassava starch. This is probably due to the genetic modification of the cassava from which the starch was isolated.

The GMCS had a swelling index value of 0.34 (Table 3). Swelling index is an indication of the quantity of liquid that can be absorbed by a material. The free energy of mixing, which causes the solvent to permeate in an effort to dilute the polymer solution, and the elastic retractile force, which opposes the deformation, are the opposing forces that determine the degree of swelling. When these two forces are balanced, swelling is considered to be in a steady state. This steady state was reached in a short time which accounted for the low swelling observed in the starch. The temperature at which swelling was observed is also an important determinant of swelling index. At higher temperatures, starches often exhibit higher swelling than at lower temperature values. The melting of crystalline region of starch results in improved swelling and this takes place above the gelatinization temperature, resulting in the leaching of amylose content (Oyeyinka *et al.*, 2015).

Table 3: Properties of genetically modified cassava starch (n =3, mean ± s.d)

BD (g/cm3)	TD (g/cm3)	HR	CI (%)	AR (°)	SI	pH	WAC (mL)
0.68 ± 0.01	0.83 ± 0.02	1.22 ±0.01	18.1 ± 0.01	39.17 ± 0.31	0.34 ± 0.05	6.7 ± 0.05	1.3 ± 0.20

BD = bulk density, TD = tapped density, HR = Hausner's ratio, AR = angle of repose, SI = swelling index, WAC = water absorption capacity

Solubility studies

The different formulated solid dispersions and the pure naproxen (NAP) were subjected to solubility test and the results are depicted in Fig. 1. It was observed that only two of the formulations S3 (0.076 mg/ml) and S8 (0.038 mg/ml) had lower water solubility than NAP

(0.105 mg/ml). Formulations in which lone polymer, GMCS or HPMC, was used generally had lower naproxen aqueous solubilities. The inclusion of polysorbate 80, a surfactant, in formulations containing polymer blends markedly increased the naproxen solubility. Solid dispersions S1 and S8 contained the same proportion of polymer blend but the former contained, in addition, 0.5g of polysorbate 80. This singular change in formulation was responsible for the significant increase in the aqueous solubility of naproxen (1.033 mg/ml). The inclusion of surfactant improves the wettability of solid dispersions (Chaudhari and Dugar, 2017) and this is responsible for the improved solubility observed with S1. The highest naproxen aqueous solubility was recorded for S2 which had a GMCS/HPMC blend ratio of 2:1, a polymer/drug ratio of 2:1 and contained 0.5g polysorbate 80.

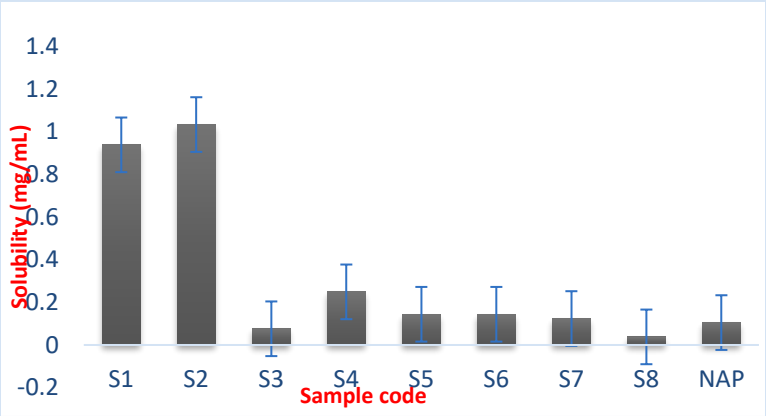

Figure 1. Solubilities of solid dispersions and pure naproxen (NAP)

Scanning electron microscopy

The scanning electron micrographs for naproxen, GMCS, HPMC and solid dispersion S2 are shown in Fig. 2. The micrograph showed naproxen particles to be flaky and with no definite shape (Fig. 2a). This is consistent with what was reported by Nupur *et al.* (2023). HPMC (Fig. 2b) also had irregularly shaped particles with rough edges. Genetically modified cassava starch had granules that were polygonal in shape and with smooth surfaces (Fig. 2c). The granular size appeared to be more uniform and with defined edges. This shape probably accounted for the fair flowability of the starch. The micrograph of the solid dispersion is shown in Fig. 2d. The particle shape appeared completely different from those of the individual constituents of the solid dispersion. Most of the particles are spherical with smooth surfaces. It appeared that the pure drug was encapsulated in the solid dispersion particles. This was expected to enhance aqueous solubility due to the proximity of the drug particles to the surface of the hydrophilic carriers.

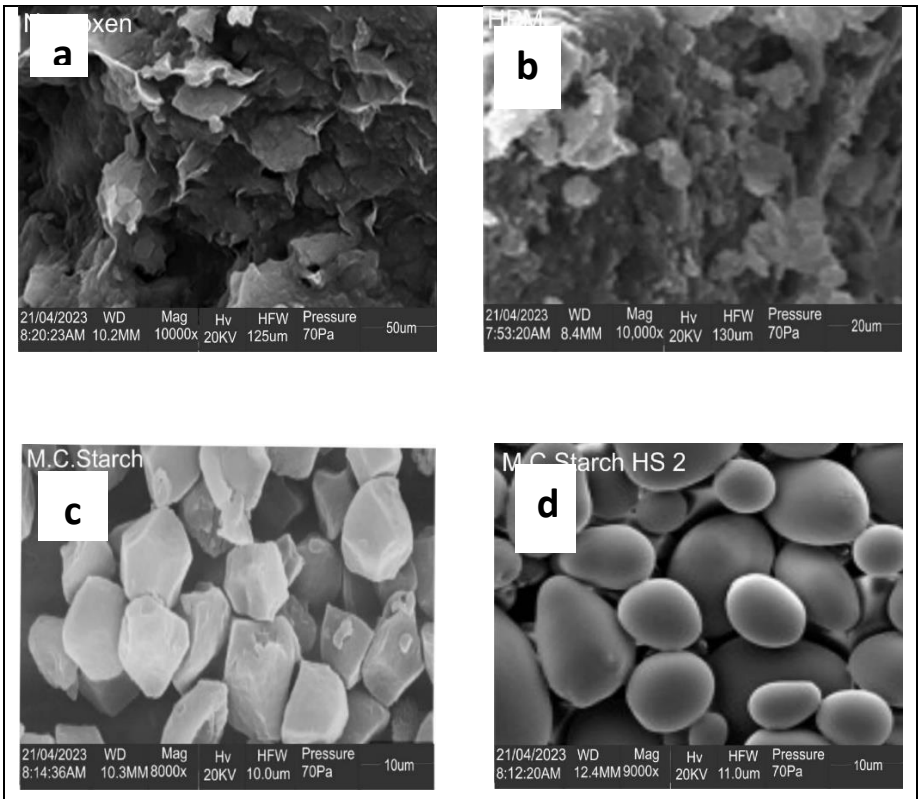

Figure 2. SEM micrograph of (a) naproxen, (b) HPMC, (c) genetically modified cassava starch (d), solid dispersion, S2.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of naproxen, GMCS, HPMC and S2 are shown in Fig. 3. The FTIR spectrum of naproxen (Figure 3b) showed characteristic peaks at 3444 cm^{-1}, 3060 cm^{-1}, 1766 cm^{-1}, 1632 cm^{-1}, 1252 cm^{-1} for -OH, $-CH_3$, -C=O, -C=C and aryl-O stretching respectively. FTIR spectrum of GMCS (Fig. 3c) showed the characteristic broad peak of -OH stretching vibration at 3280 cm^{-1}, -CH stretching at 2929 cm^{-1} and -C=O stretching at 1647 cm^{-1}. The spectrum of solid dispersion S2 (Fig. 3d) showed that there was no significant interaction between the polymers and the drug. The characteristic peaks associated with naproxen functional groups are largely retained in the solid dispersion.

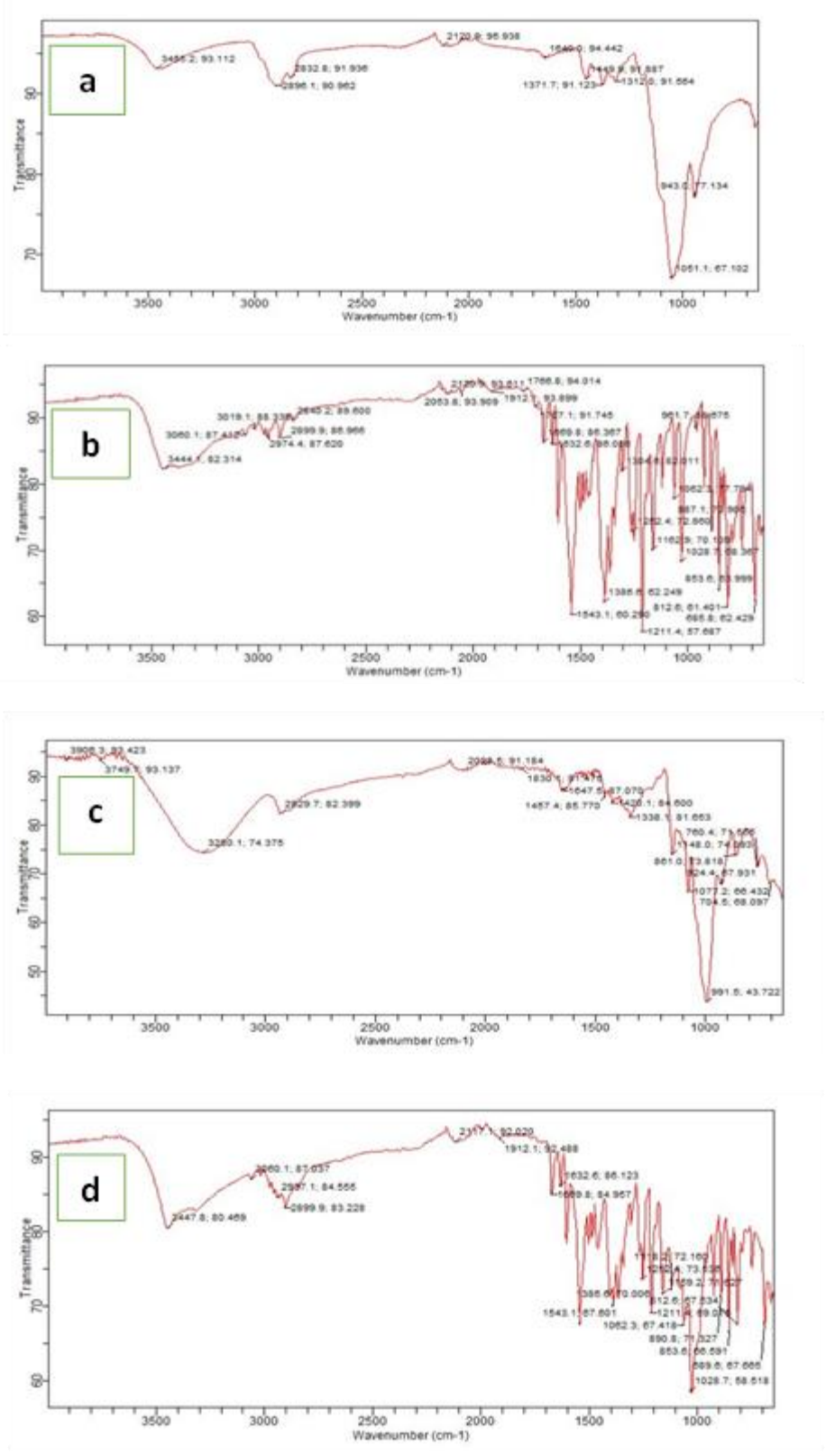

Figure 3. FTIR spectra of (a) HPMC, (b) Naproxen, (c) genetically modified cassava starch, (d) solid dispersion S2.

Differential scanning calorimetry

The DSC thermograms of naproxen, GMCS, HPMC and S2 are indicated in Fig. 4. The endothermic peak associated with naproxen was not seen in the thermogram of the solid dispersion. This is an indication that the state of naproxen changed into an amorphous form in the solid dispersion matrix (Fig. 4d).

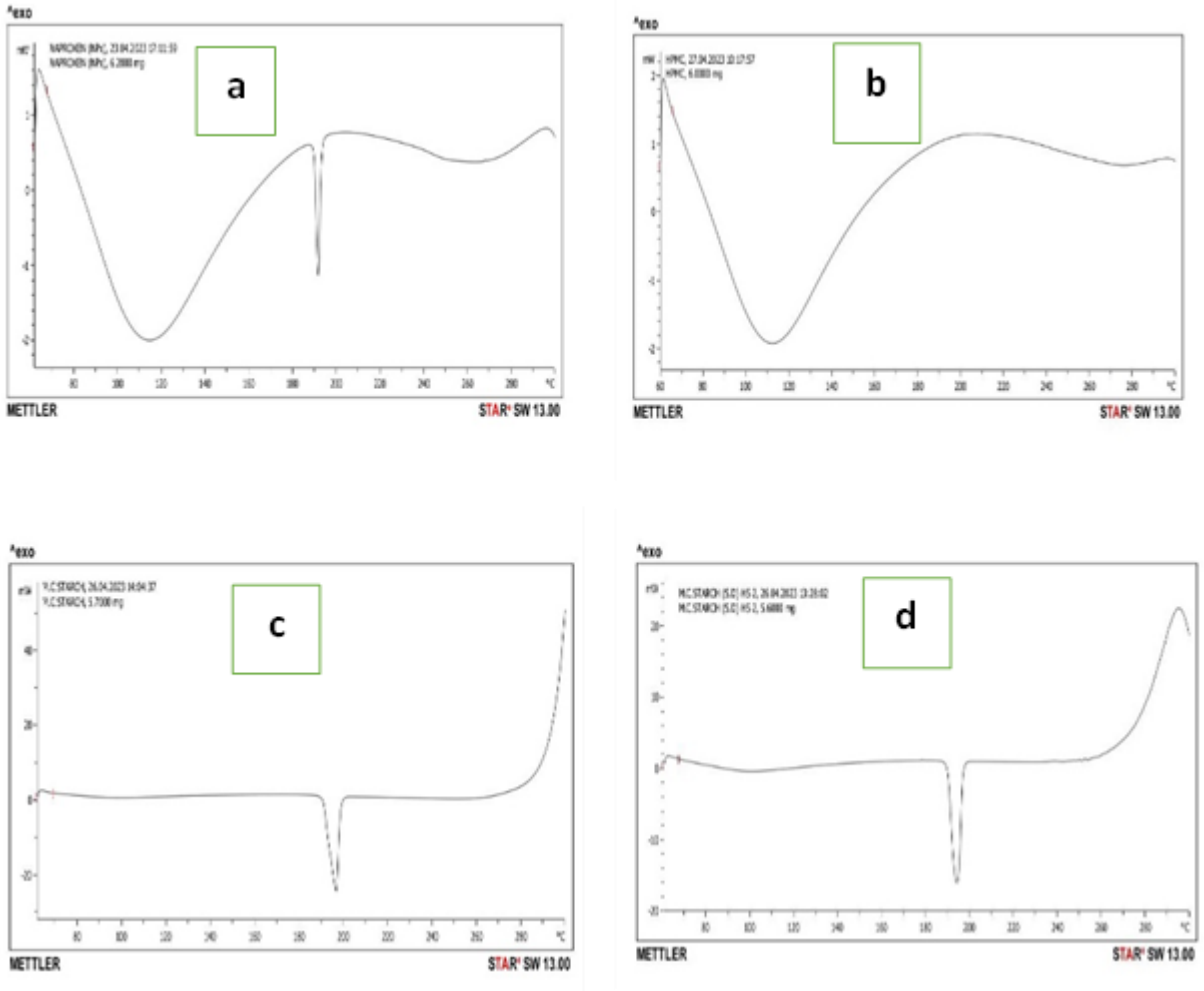

Figure 4 DSC thermogram of (a) naproxen, (b) HPMC, (c) genetically modified cassava starch, (d) Solid dispersion S2.

Tablet properties

Solid dispersion S2 was formulated into tablets (T2) by direct compression. Tablets of pure naproxen (TN) were also compressed. The properties of these tablets were assessed.

Hardness, friability and weight uniformity

The hardness, friability and weight uniformity results for the tablets of solid dispersion (T2) and pure naproxen (TN) are shown in Table 4. The hardness of the tablets was respectively 5.1 and 7 kg/cm^3 for T2 and TN. The evaluation of tablet hardness is important to assess the integrity of tablets during storage and transportation (Induri *et al.*, 2012). Hardness affects other tablet properties like disintegration as tablets that are too hard may have delayed disintegration time (Pisek *et al.*, 2002). The two samples under investigation had hardness values that were within the acceptable limits set by the British Pharmacopeia.

Friability test is carried out to examine the ability of the tablets to withstand shock and attrition during the manufacturing process and handling. The standard specified in the British Pharmacopeia for percentage friability of an ideal tablet is less than 1%. Solid dispersion tablet T2 and naproxen tablet, TN had percentage friability of 10.59% and 11.17% respectively. Both tablet preparations did not meet the standard specified in the British Pharmacopeia. The implication is that both tablets are susceptible to chipping, breaking or capping under the influence of mechanical stress. The high friability values may be due to inadequacy of the compression pressure applied during tablet (Paul & Sun, 2017). None of the tablets

had a value of more than ±5 and therefore passed the weight uniformity test.

Disintegration time

Disintegration is the mechanical breakdown of a tablet into granules upon swallowing, resulting in the breakdown of the inter-particulate bonds created during tablet compression. The breakdown period of uncoated tablets should be less than 15 minutes, according to specified limits in the British Pharmacopoeia. The plain naproxen tablet formulation, TN, had a disintegration time of 9.49 minutes and the solid dispersion tablet formulation, T2, had a disintegration time of 13.38 minutes (Table 4). Both formulated tablets conformed to the established criterion for disintegration time. The longer time needed for the solid dispersion tablet formulation T2 to dissolve could be attributed to the longer time needed for the polymer-drug matrix to wick in fluid and weaken the inter-particulate bond.

Drug release

The tablets showed varying drug release patterns. The results are shown in Table 4. The t_{50} and t_{90} values for T2 and TN varied significantly. T2 released 50% of the drug content in less than 5 min while it took TN almost 29 min to achieve the same drug release. The t_{90} for the tablets were 37.72 min and 63.42 min for T2 and TN respectively. Tablet T2 released naproxen more quickly than TN due to higher aqueous solubility of naproxen in the former. The solid dispersion tablet therefore offered a potential faster onset of action, compared to the plain tablet. The drug release from the tablets when fitted into the Korsemeyer-Peppas model of release kinetics showed that the release exponents (n values) of the tablets were different, indicating different release mechanisms. The mechanism of release of naproxen from TN ($n = 0.744$, $R^2 = 0.9957$) occurred by both diffusion and erosion (non-Fickian transport) while the release from T2 ($n = 0.2278$, $R^2 = 0.9791$) occurred by Fickian diffusion in which the drug is released by diffusion through the matrix of the tablet (Paarakh *et al.*, 2018).

Table 4: Properties of solid dispersion and naproxen tablets (n=3, mean ± SD)

Formulation	T2	TN
Hardness (Kg)	5.1 ± 0.1	7 ± 0.3
Friability (%)	10.68 ± 0.28	11.59 ± 0.41
Weight Uniformity (%)	< ±5	< ±5
Disintegration Time (mins)	9.60 ± 0.49	13.64 ± 0.45
T_{50} (mins)	4.90 ± 0.40	28.80 ± 0.50
T_{90} (mins)	37.24 ± 0.34	63.80 ± 0.29

T2 = tablet of solid dispersion S2, TN = tablet of pure naproxen.

CONCLUSION

The genetically modified cassava starch possessed a flow characteristic that is suitable for use as excipient for tableting. The starch, when blended with HPMC, is suitable for use as a hydrophilic carrier for solid dispersion matrix. The inclusion of polysorbate-80 to the blend of genetically modified cassava starch and HPMC offered synergy to the effectiveness of these polymers as naproxen solubility enhancer.

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