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Enhancement of Naproxen Solubility via Solid Dispersion using Ipomoea Batatas Starch – Hydroxypropyl Methyl Cellulose Polymer Blends and Polysorbate 80

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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 the article.

Abstract

Background: Naproxen's poor aqueous solubility limits its oral bioavailability, posing formulation challenges. This study aimed to improve its solubility by formulating a ternary solid dispersion (SD) using blends of Ipomoea batatas starch (PS) and hydroxypropyl methyl cellulose (HPMC), including polysorbate 80 as surfactant.
Materials and Methods: The flow property of PS was assessed by Carr's index (CI) and Hausner's ratio (HR). Naproxen SD was prepared via solvent evaporation using varying drug/polymer ratios. The SD with the highest aqueous solubility was characterised by scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FTIR). Tablets of both optimum SD (T6) and pure naproxen (TN) were prepared by direct compression and assessed for friability, hardness, dissolution and weight uniformity.
Results: Potato starch had a Hausner's ratio of 1.17 ± 0.01, indicating good flow. The highest aqueous solubility was observed for a drug/polymer ratio of 1:4, with the PS/HPMC ratio being 1:3 (S6). Polysorbate 80 increased solubility by up to four times. SEM micrographs of the SD showed no trace of naproxen, suggesting a loss of the drug's crystalline structure, while DSC confirmed decreased crystallinity. FTIR spectra showed that the structure of naproxen was not altered by the solid dispersion. The optimal SD tablets met acceptable standards. The T50 drug release time was 9 minutes, compared to 29 minutes for TN. There was synergism between PS and HPMC in enhancing naproxen solubility, which was further improved by the addition of polysorbate 80.
Conclusion: Naproxen's solubility in solid dispersion improved due to polymer blending and was further improved by the addition of polysorbate 80 as a surfactant.

Keywords: Ipomoea batatas starch, solid dispersion, naproxen, hydroxypropyl methyl cellulose, polysorbate 80

INTRODUCTION

Solubility behaviour is one of the main problems that drug design and the development of new chemical entities encounter. Drugs that are highly soluble in the gastrointestinal tract exhibit absolute oral absorption and good bioavailability. The solubility of drugs is an essential facet of drug study, lead molecule design, and drug development. An active pharmaceutical ingredient's solubility is one of the major factors that modulate the attainment of appropriate systemic drug concentration. Improving the solubility and

dissolution rate of poorly water-soluble drugs, as well as increasing the permeability of those that are poorly permeable, are critical focuses of pharmaceutical research aimed at enhancing oral bioavailability (Aggarwal et al., 2010).

Many techniques are available to improve the solubility and rate of dissolution of poorly soluble drugs. Particle size reduction increases the surface area and dissolution. The process of size reduction, such as milling, however, induces physical stress on the drug and facilitates degradation. Milling also makes the amorphous region of the drug prone to recrystallisation at high temperatures (Yiyun et al., 2005). Micronisation can also lead to particle aggregation and poor particle wettability. The use of salt formation techniques to increase the dissolution rate is also problematic in that it does not apply to neutral compounds. Even when salts are formed, an enhanced dissolution rate cannot be guaranteed because of the possibility of the salts reverting to their acid and base forms. Salts can also react with water and carbon dioxide to cause precipitation of the active agent (Babu et al., 2002). Solid dispersion techniques ameliorate the challenges associated with the other techniques. Synthetic carriers such as crospovidone (Ganapuram et al., 2013); polyvinylpyrollidone (Adil et al., 2021); poly(ethyleneglycol) (Alshehri et al., 2020); Eudragit and poly(vinylpyrrolidone-co-vinyl acetate) (Trasi et al., 2020); have been evaluated as carriers in solid dispersion. Plant polysaccharides are gaining more attention as carriers because of their ready availability, cost advantage, non-toxicity, biocompatibility and degradability (Gopinath et al., 2018; Slima et al., 2019).

Starch is second only to cellulose as the most abundant biomaterial in nature. Starch is hydrophilic and possesses unique characteristics that have endeared it to applications in pharmaceuticals and other fields (Maniglia et al., 2021). Activities of starch are often enhanced by blending with other polymers such as hydroxypropyl methylcellulose (Ayorinde et al., 2016). The dissolution of solid dispersion is also enhanced using a blend of two hydrophilic polymers as drug carriers (Ohyagi et al., 2017). Naproxen is a class II drug of the Biopharmaceutical Classification System (BCS) and a non-steroidal anti-inflammatory drug of the 2-aryl propionic acid class. It is used in managing pain and inflammatory diseases such as osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. The pharmacological activity of naproxen is, however, limited by its poor aqueous solubility, with dissolution being the rate-limiting factor for its bioavailability (Tsume et al., 2014). Few studies have attempted to enhance the drug's solubility through solid dispersion formulations using a biodegradable polymer. Sodium starch glycolate, a modified starch, blended with polyethylene glycol, has successfully served as a carrier for naproxen (Nupur et al., 2023). Other works have utilised synthetic polymers as hydrophilic carriers in solid dispersion formulation (Ueda et al., 2018; Shibata et al., 2022). There are, however, increasing concerns about the toxicity of synthetic polymers (Satchanska et al., 2024). Native starches, considered safe and non-toxic, remain largely unevaluated as hydrophilic carriers for solid dispersion. Surfactants (such as polysorbate 80) can enhance wettability in solid dispersion (Chaudhari and Dugar, 2017) and thereby have the potential to increase drug solubility. In this work, we attempted to prepare and evaluate a ternary solid dispersion of naproxen using blends of native Ipomoea batatas (sweet potato) starch (PS) and hydroxypropyl methyl cellulose (HPMC) as carriers, and polysorbate 80 as a surfactant to improve its aqueous solubility

MATERIALS AND METHODS

Materials

Naproxen powder (Shandong Huashang Chemical Co. Ltd (China)); CAS No.: 22204-53-1.

Polysorbate 80 (Tween® 80 Pharmaceutical standard) purchased from Sigma-Aldrich (Germany); CAS No.: 9005-65-6.

Ethanol (Merck, Germany); CAS No.: 64-17-5.

HPMC (5mPa.s) purchased from Zhejiang Haishen Chemical Co. Ltd. (China); CAS No.: 9004-65-3.

Ipomoea batatas (white sweet potato variety) tubers were sourced from Bodija, Ibadan (7.434049,3.913990).

All reagents used are of analytical grade.

Methods

Sample preparation

Starch was isolated using a previously described method with minor adjustments (Wickramasinghe et al., 2009). The sweet potato tubers were peeled, cut into smaller pieces and then blended with distilled water for 5 minutes using a laboratory blender (Binatone BLG-605ss). The slurry was strained using a muslin cloth and the filtrate allowed to stand for 2 hours at room temperature. The supernatant was subsequently decanted and the sediment rinsed several times using distilled water and dried to constant weight at 55 oC in an oven. The dried mass was size-reduced with a laboratory blender (Binatone BLG-605ss), passed through a 120-mesh screen and stored in an airtight container.

Characterisation of native potato starch

Bulk density, Tapped density, Hausner's ratio (HR) and Carr's index (CI)

A 30 g quantity of native sweet potato starch was weighed and poured into a 100 mL measuring cylinder. The initial volume, V0, occupied by the sample was determined. To determine the tapped volume, the measuring cylinder was tapped 100 times at 38 taps per minute, after which the tapped value was recorded and the volume occupied V100 was determined. The bulk and tapped densities were estimated as the ratio of the weight of the samples to the volume (V0 and V100, respectively). HR and CI were calculated as follows;

HR= (tapped density)/(bulk density) (1)

CI= ((tapped density - bulk density) x 100)/(tapped density) (2)

Angle of Repose

This was measured following the method described by Iwuagwu and Onyekweli (2002), with minor modifications. Fifteen grams of sweet potato starch was poured into a cylinder placed on a horizontal base of known diameter. The cylinder was gradually removed to leave a powder cone on the horizontal surface. The cone height, h, was determined and the angle of repose, θ, was calculated using the expression;

$\tan \theta = \text{height/radius}$ (3)

Particle size

The average particle size was determined with the aid of an optical microscope (MT3300EXXII, Microtrac Bel, Japan). The starch sample was thinly spread on a slide and observed under the digital microscope at a magnification of x400. Measurement of the particle diameters of 100 particles was taken with TS View CX Image® software (v. 6.2.4.3) and Motic Image 2000 (Motic China Group Co., Ltd., Xiamen, China). The mean particle size of the starch was determined using GraphPad Prism v. 8.0.1 (GraphPad Software, San Diego, USA).

Preparation of naproxen solid dispersion

Naproxen SD was prepared by the solvent evaporation method. The solid dispersion was prepared using PS and HPMC as carriers, and polysorbate 80 as a surfactant. The constituents of the different SD formulations are shown in Table 1. An appropriate amount of polysorbate 80 was added to 80 % ethanol, and the solution was added to a mixture of appropriate quantities of naproxen, PS and HPMC in a 100 mL beaker. The dispersion was stirred continuously on a magnetic stirrer until the solvent evaporated. The resulting paste was oven-dried (Gallenkamp BS 250 size 1; Gallenkamp Labs, London, UK) at 60 °C. It was then pulverised and passed through a 60-mesh screen.

Naproxen solid dispersion tablet preparation

Solid dispersion equivalent to 100mg of naproxen was directly compressed into tablets. Other excipients used in the compression of tablets are magnesium stearate, calcium carbonate and cornstarch (Table 2). The compression was at a compression force of 1.00 Nm using a single-punch hydraulic tabletting press (Model 38510E, Carver Inc., USA). The tablets of the solid dispersion with the optimum solubility, S6 (T6) and pure naproxen (TN), were compressed.

Table 1: Formulation table for solid dispersion

Formulation	S1	S2	S3	S4	S5	S6	S7	S8
Naproxen (g)	2	2	2	2	2	2	2	2
Sweet potato starch (g)	1.33	2.67	6	2	4	2	-	1.33
HPMC (g)	0.67	1.33	2	-	-	6	2	0.67
Polysorbate 80	0.5	0.5	0.5	0.5	0.5	0.5	0.5	-
Polymer:Drug Ratio	1:1	2:1	4:1	1:1	2:1	4:1	1:1	1:1

Table 2: Tablet formulation

Formulation	Nap1 (g)	MS (g)	CS (g)	CC (g)
T6	0.46	0.01	0.01	0.02
TN	0.10	0.05	0.05	0.30

T6 – Tablet of solid dispersion S6; TN – Tablet of pure naproxen; MS = Magnesium stearate; CS = corn starch; CC = calcium carbonate; Nap1 – 0.1g naproxen equivalent.

Characterisation of solid dispersion

Differential scanning calorimetry
A differential scanning calorimeter (TA-60, Shimadzu) was used to obtain DSC thermograms for the samples. The samples (10 mg) were placed in a sealed aluminium pan under nitrogen flow (at 20 mL/min). The pan was heated over a 40 – 240 oC temperature range and at an increment rate of 5 oC/min.
Fourier transform infrared (FTIR) spectroscopy
An FTIR spectrophotometer was used to obtain FTIR spectra of NAP, PS, HPMC and SD. The samples were each mixed with KBr pellet and the samples scanned over a frequency range of 400-4000 cm-1.

Scanning electron microscopy (SEM)
The surface granular morphology of the samples was examined using a scanning electron microscope (Hitachi S-34000N, Japan). Adhesive tape was used to fix the samples on a brass stub. The samples were made electrically conductive with the aid of platinum (6nm/min) coating in a vacuum. Hitachi Ion Sputter (E-1030) was used to achieve this at 15mA and for 240 seconds.

Solubility
For the solubility test, 50 mg of the various solid dispersion samples were transferred into a 100 mL beaker containing 50 mL of distilled water. The dispersion was placed on a magnetic stirrer and stirred for 10 hours at a constant temperature of 30 °C. After filtration, 0.5 mL of the supernatant was removed using a micropipette and analysed using a UV-visible spectrophotometer (Spectrumlab 752 s) at a wavelength of 480 nm to determine the concentration of naproxen.

Evaluation of solid dispersion and pure naproxen tablets
Tablet Friability
A friability tester was employed to check the friability of the tablets. Ten previously weighed tablets were put in the friability tester and subjected to repeated shocks by rolling. After four minutes of treatment equivalent to 100 revolutions, the tablets were weighed and the percentage of friability was determined thus;

$$F = (M1-M2)/M1 \times 100 \quad (4)$$

F = Percentage friability of the tablet;
M1 = initial weight of the tablets
M2 = final weight of the tablets

Tablet Hardness
The tablets' hardness was evaluated by the diametrical compression method using a hardness tester (Ketan, Mumbai, India).

Weight variation of tablets
Using an analytical balance, ten pills from each batch were weighed to determine the average weight of the batch. Each of the tablets was weighed separately, and the percentage of weight variation from the mean was obtained.

Tablet Disintegration
The test was done using a Veego tablet disintegration test apparatus (Veego Instruments, India). The beakers and the disintegration medium (distilled water) were allowed to warm to 37 °C. The sample tablets were subsequently placed in the baskets, and the time taken for complete disintegration and passage through the basket was noted.

Tablet Dissolution
Compressed tablets of the most soluble SD (T6) and pure naproxen (TN) were analysed for drug release. The dissolution test was carried out with a Copley DIS 6000 tablet dissolution apparatus. Each sample, equivalent to 100 mg of naproxen, was added to 900 mL of the phosphate buffer (pH 7.2) dissolution medium. The dissolution was done at 37 ± 0.5 °C and 100 rpm. Every 5 minutes, 5 mL of the dissolution medium was sampled, filtered and absorbance measured using a UV–Vis spectrophotometer (Spectrumlab 752 s) at wavelength 480 nm. Five (5 mL) of fresh buffer was replaced with every 5 mL sample withdrawn.

Data analysis

Results are presented as the means of triplicate values ± standard deviation. Statistical significance was tested by Student's t-test using GraphPad Prism 10 (GraphPad Software, Inc., San Diego, USA).

RESULTS

Physicochemical properties of potato starch

The physicochemical properties of PS are shown in Table 3.

Evaluation of solid dispersion

Solid dispersion solubility

Figure 1 shows that solid dispersion S6 (which contained a polymer/drug wt% of 80 %; polysorbate 80 at polysorbate 80/polymer wt% of 0.59 % and PS/HPMC at wt% of 33.33 %) exhibited the highest solubility, which was about six-fold the solubility of pure naproxen. The ranking order of solubility of the solid dispersion preparations was S6 > S1 > S2 > S8 > S3 > S4 > S7 > S5. Generally, the solid dispersion preparations had higher solubility than the pure drug. The highest solubility of naproxen was recorded with the highest polymer/drug wt% (80 %) in the system. The lowest solubility values were recorded for solid dispersions in which only one polymer was used as the carrier (S4, S5, and S7). Higher aqueous solubility was observed in S1, compared to S8. The inclusion of polysorbate 80 in the S1 formulation enhanced solubility by up to threefold.

Scanning electron microscopy (SEM)

The SEM micrographs of NAP, PS, HPMC and S6 are depicted in Figure 2a-d. The crystals of naproxen are seen in Figure 2a. The naproxen particles had no definite shape and appeared flaky. The granules of the PS were shown to be mostly oval with smooth surfaces and defined edges, and little aggregation (Figure 2b). The granules of HPMC also appeared to possess rough surfaces with no definite shape (Figure 2c). The micrograph of the solid dispersion S6 (Figure 2d) appeared in clusters with attendant rough surfaces.

Table 3: Physicochemical properties of potato starch (n=3, mean ± SD)

BD (g/cm^3)	TD (g/cm^3)	CI (%)	HR	AR (°)	MPS (µm)
0.58 ± 0.01	0.68 ± 0.01	14.7 ± 0.22	1.17 ± 0.01	33.82 ± 0.20	23.1 ± 7.18

BD – Bulk density, Tapped Density, Carr's Index, AR – Angle of repose, MPS – Mean Particle size.

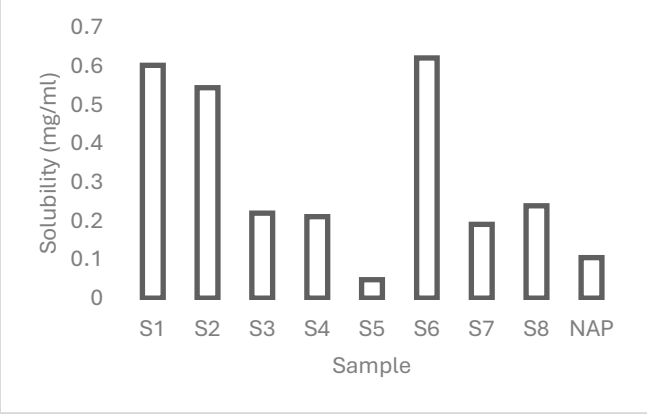

Figure 1. Solubility values of solid dispersion formulations and pure naproxen

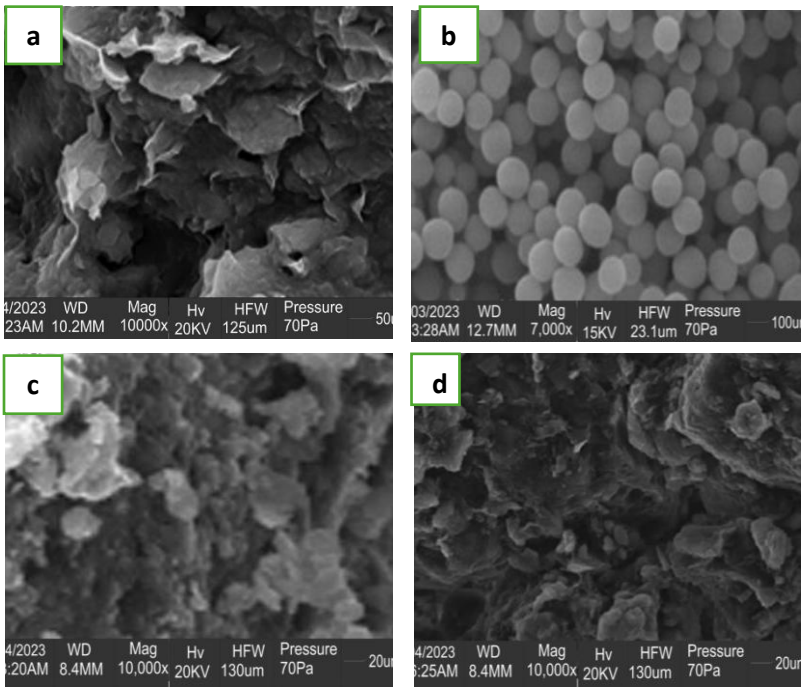

Figure 2. SEM micrographs of (a) Naproxen (b) Sweet potato starch (c) HPMC (d) solid dispersion S6

Differential scanning calorimetry (DSC)

The DSC thermograms of naproxen, potato starch, HPMC and solid dispersion are depicted in Figure 3a-d. A sharp endothermic peak corresponding to naproxen melting was shown at 193 °C (Figure 3a). The endothermic peak characteristic of the melting of the pure crystalline naproxen was conspicuously absent in the solid dispersion's thermogram (Figure 3d). However, a sharp endothermic peak was observed at a lower energy of 93 ºC.

Fourier-transform infrared spectroscopy (FTIR)

The spectra for naproxen, sweet potato starch, hydroxypropyl methylcellulose and solid dispersion are depicted in Figure 4a-d. Naproxen spectra displayed characteristic peaks around 1707 cm-1 (C=O stretching), 3447 cm-1 (OH stretching), 1632 cm-1, 1481 cm-1 (C=C aromatic stretching) and 1252 cm-1 & 1028 cm-1 (=C-O-C stretch) (Nupur et al., 2023). The spectrum from the solid dispersion formulation S6 largely displayed the characteristic peaks associated with naproxen and the carriers.

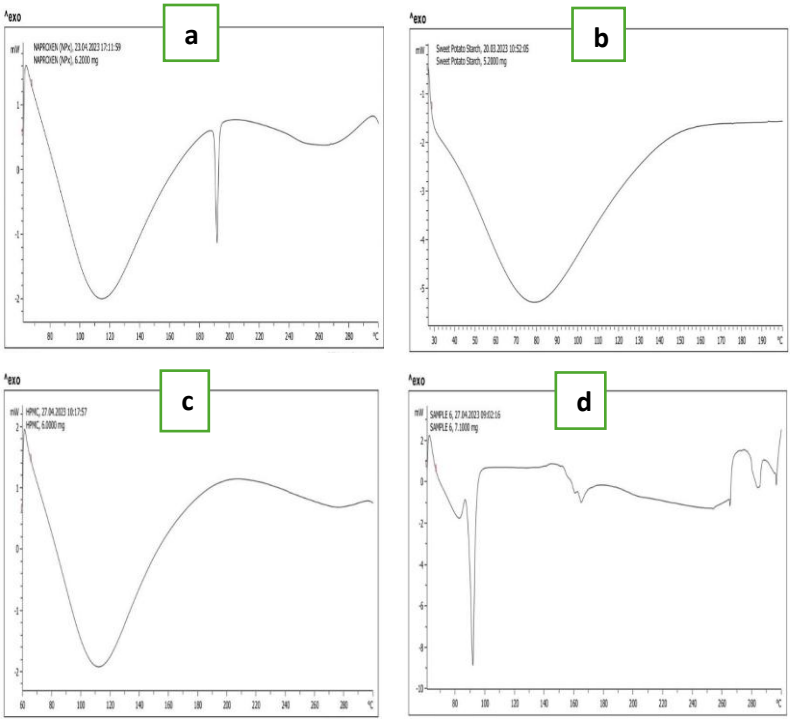

Figure 3. DSC thermogram of (a) Naproxen (b) Potato starch (c) HPMC (d) S6

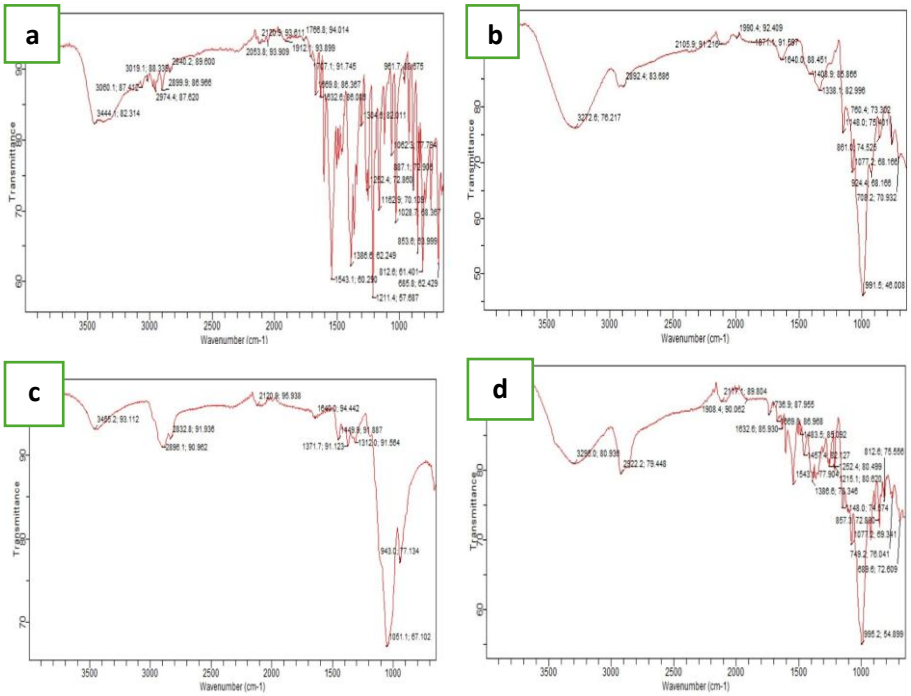

Figure 4. FTIR spectra of (a) Naproxen (b) potato starch (c) HPMC (d) solid dispersion S6

Evaluation of the solid dispersion and pure naproxen tablets

Results for the mechanical and release properties of the tablets are listed in Table 4. The tablet formulation containing solid dispersion of optimum solubility (T6) exhibited acceptable hardness and friability (hardness value between 5 – 10 N and friability < 1 %). The values of hardness and friability for pure naproxen tablets (TN) fall outside the acceptable values. Both tablet formulations passed the weight uniformity test, as none had values greater than 3 % and 4 % for T6 and TN, respectively.

Tablets TN and T6 exhibited disintegration times of less than 15 minutes, thus falling within the acceptable range. T6 took longer to disintegrate compared to TN. The dissolution profiles of T6 and TN are displayed in Figure 5. The cumulative amounts of naproxen released after 5 minutes were approximately 34.72 % and 11.32 % for T6 and TN, respectively. Fifty per cent (50 %) of the drug in T6 and TN was released within 9 minutes and 29 minutes, respectively. Also, at the end of 60 minutes, 99 % of naproxen had been released from T6, compared to 85 % from TN.

Table 4: Mechanical and release properties of solid dispersion and pure naproxen tablets. (n = 3, mean ± *SD*)

Formulation	Hardness (N)	Friability (%)	t_{50} (mins)	t_{90} (mins)	DT (mins)
T6	6.67 ± 0.58	0.96 ± 0.01	9	28	14.00 ± 1.00
TN	4.33 ± 0.58	10.26 ± 0.27	29	63	9.67 ± 1.53

T6 – Tablet of naproxen solid dispersion S6; TN – tablet of pure naproxen; DT – Disintegration time.

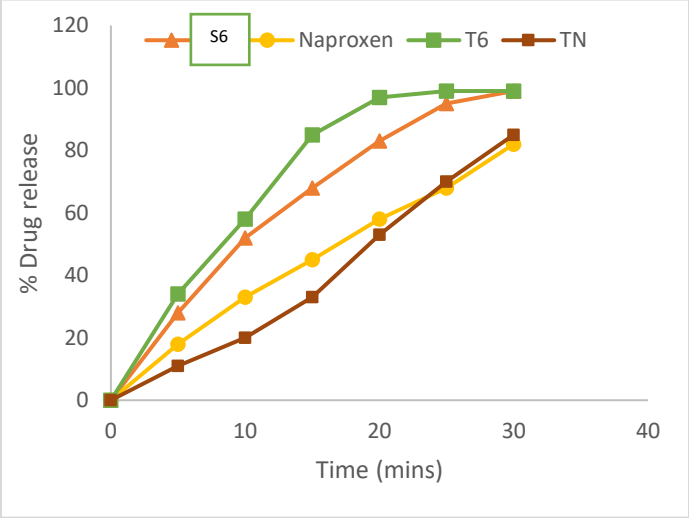

Figure 5. Dissolution profile of solid dispersion (S6), pure naproxen (Naproxen), solid dispersion tablet (T6) and pure naproxen tablet (TN)

DISCUSSION

Hausner's ratio of 1.17 ± 0.01 suggests a good flow. Hausner's ratio and Carr's index are pointers to the flowability and compressibility of powders. Hausner's ratio values of less than 1.25 are considered to have good flow properties, while powders with Carr's index values below 15 are also deemed to be good flowing; those with values exceeding 25 are classified as poor flowing (Ayorinde *et al.*, 2013). The result of Carr's index of PS showed that the starch had a good flow. These results are consistent with those obtained in a previous study (Yusuf *et al.*, 2022). The angle of repose also gave an indication of good flowability. The good-flowing nature of the starch may be attributed to the size and the oval and evenly sized nature of the starch granules. The mean particle size of PS (Table 3) was higher than the granules of a commercial cultivar (3.1 µm) reported earlier (Shen *et al.*, 2022), lower than that reported by Zhu and Hao (2019), but similar to that reported by Sanchez-Gonzalez *et al.* (2019). Li *et al.* (2023) reported varying environmental conditions such as temperature, drought and fertiliser regimes as factors that influence granule size. The starch extraction methods could also influence the particle size of potato starch (Neeraj *et al.*, 2021).

The increased solubility observed in the solid dispersion, compared to the pure drug, suggests that the aqueous solubility of naproxen was improved by the formulation of solid dispersion. The major influences on the solubility are polymer/drug and polymer blend wt%. Polymer/drug ratio has a strong influence on drugs' dissolution rate in solid dispersion formulations (Van Duong & Van der Mooter, 2016). The synergy between PS and HPMC aligned with an earlier work in which the synergistic effect of HPMC and Eudragit® S on dissolution was reported (Ohyagi *et al.,* 2017). This synergy is believed to be due to molecular interaction between the polymers, resulting in enhanced solubility (Ueda *et al.,* 2018). The higher solubility value observed for S1, compared to S8, showed the influence of polysorbate 80 in the enhancement of solubility. The observed increased solubility enhancement due to the inclusion of polysorbate 80 can be attributed to the promotion of wettability by the surfactant (Li *et al.*, 2023). A similar influence of polysorbate 80 on solubility has been reported earlier (Balogun-Agbaje *et al.*, 2023).

The morphology of PS is similar to that previously reported (Wong *et al*., 2021). The individual structural morphologies of PS and HPMC are not notable in the solid dispersion micrograph. This could be a result of the interaction between the polymers. There appeared to be no significant traces of naproxen on the micrograph, suggesting that the drug was dispersed in the matrix of the polymer blend.

In the DSC thermogram, the sharp endothermic peak at 193 °C for naproxen is an indication of the crystallinity of the drug. The absence of this peak in the solid dispersion thermogram, but the appearance of an endothermic peak at a lower energy (93 ºC), may be due to a reduction in crystallinity of naproxen.

The presence of characteristic peaks of both naproxen and the carriers in the solid dispersion FTIR spectrum indicates that no significant interaction existed between the drug and the polymers.

The mechanical properties of tablets are important determinants of the tablet's integrity during manufacture, storage, distribution and use. Tablets are expected to be hard enough to withstand the stress and shock associated with handling, yet not too hard to prevent disintegration. Tablet T6 thus possessed the ability to withstand stress associated with handling. The improved hardness and friability observed with T6 may be due to better packing of the granules during the tablet compression process. Disintegration time is the time taken for the tablet to be completely broken down into granules. The BP recommends that the disintegration time for uncoated tablets should not be up to 15 minutes. The longer disintegration time of T6 compared to TN may be attributed to a longer duration required for fluid penetration into the polymer-drug matrix of the tablets, owing to effective packing and hardness. The faster onset of drug release and the eventual increase in the rate of dissolution of T6 were due to the increase in solubility of naproxen due to the formulation of the drug into solid dispersion.

CONCLUSION

The characterisation of potato starch used in the formulation of naproxen solid dispersion showed that the starch possessed good flow properties and could be effectively blended with hydroxypropyl methyl cellulose to enhance naproxen solubility. Naproxen's solubility in solid dispersion formulation was enhanced by the combination of hydroxypropyl methyl cellulose and sweet potato starch, but the solubility was further enhanced by the inclusion of polysorbate 80. Consequently, a ternary solid dispersion comprising a blend of potato starch and HPMC, along with the addition of polysorbate 80, has the potential to enhance the aqueous solubility of naproxen.

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