Enhancement of cefixime solubility using a ternary solid dispersion system containing starch isolated from maize genotype

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ABSTRACT

Background: Cefixime is a third-generation cephalosporin that has poor solubility and low bioavailability.

Objectives: This study aimed to formulate cefixime as solid dispersion using a blend of starch isolated from maize genotype and hydroxypropyl cellulose (HPC) to enhance its solubility and thus improving its oral absorption.

Methods: The solubility and dissolution rate of solid dispersion formulations prepared by solvent evaporation method were measured. The morphology, spectroscopic and thermal properties of the optimum formulation were determined. Tablets containing the optimum formulation were directly compressed and evaluated.

Results: The optimum formulation exhibited a good dissolution profile and had an enhanced solubility of 15.2± 0.23 mg/mL which was thrice as much that of plain cefixime. Fourier transform infrared spectra showed there was no interaction between the drug and the polymers. X-ray diffraction pattern reveals that cefixime was transformed into a highly amorphous material due to the formation of solid dispersion. The time taken for 50 % (T_{50}) and 90 % (T_{90}) drug release were higher than that of tablets containing plain cefixime.

Conclusion: The results showed that the solid dispersion formulations improved the drug's solubility and could be explored in the controlled release of cefixime.

Keywords: cefixime, aqueous solubility, solid dispersion, maize genotype, starch

Amélioration de la solubilité du céfixime à l'aide d'un système de dispersion solide ternaire contenant de l'amidon isolé à partir d'un génotype de maïs

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RÉSUMÉ

Contexte: Le céfixime est une céphalosporine de troisième génération qui présente une faible solubilité et une faible biodisponibilité.

Objectifs: Cette étude vise à formuler le céfixime sous forme de dispersion solide en utilisant un mélange d'amidon isolé du génotype de maïs et d'hydroxypropylcellulose (HPC) pour augmenter sa solubilité et ainsi améliorer son absorption orale.

Méthodes: le taux de dissolution et la solubilité des formulations de dispersion solide préparées par la méthode d'évaporation du solvant ont été mesurées. Les propriétés morphologiques, spectroscopiques et thermiques de la formulation optimale ont été déterminées. Les comprimés contenant la formulation optimale ont été directement compressés et évalués.

Résultats: La formulation optimale présentait un bon profil de dissolution et avait une solubilité accrue de 15,2 ± 0,23 mg/mL, soit trois fois celle du céfixime ordinaire. Les spectres infrarouges à transformée de Fourier ont montré qu'il n'y avait pas d'interaction entre le médicament et les polymères. Le diagramme de diffraction des rayons X révèle que le céfixime s'est transformé en un matériau hautement amorphe en raison de la formation d'une dispersion solide. Les délais de libération du médicament à 50 % (T_{50}) et 90 % (T_{90}) étaient supérieurs à ceux des comprimés contenant du céfixime ordinaire.

Conclusion: Les résultats ont montré que les formulations en dispersion solide amélioraient la solubilité du médicament et pouvaient être explorées dans le cadre de la libération contrôlée du céfixime.

Mots clés: céfixime, solubilité aqueuse, dispersion solide, génotype de maïs, amidon

INTRODUCTION

The oral route is the most common and convenient method of drug delivery due to its numerous advantages which include versatility, safety and enhanced patient compliance.[1] However, drugs with poor water solubility will typically exhibit a dissolution rate limited absorption when administered orally thus requiring high doses to give the desired therapeutic effect which could result in toxicity problems. Cefixime is a third-generation cephalosporin that is indicated in the treatment of gonorrhoea, uncomplicated urinary tract infections, otitis media and lower respiratory tract infections. It was the first oral third-generation cephalosporin that had the same activity as the parenteral to be developed.[2] It belongs to the class II group of drugs as per the Biopharmaceutics Classification System (BCS) because of its poor solubility and high permeability.[3] As a result of its low solubility, its bioavailability is only 30-50 % of an oral dose absorbed and it exhibits a maximum peak serum concentration within 2-6 hours.[4] Hence, there is a need to develop a delivery system to overcome these shortcomings. Several approaches namely nanoparticle formation, co-solvency, micronization, salt formation, complexation with cyclodextrin and solid dispersion have been developed to improve the solubility and bioavailability of poorly soluble drugs with the solid dispersion (SD) technology standing out as a highly effective method.[5] Solid dispersion (SD) is a dispersal in the solid state of a drug in a hydrophilic polymer matrix with (ternary solid dispersion) or without (binary solid dispersions) the addition of a surfactant. Ternary solid dispersions have been reported to enhance the solubility and dissolution of BCS class II drugs more than binary solid dispersions.[6] The classical methods of preparing SD are lyophilization technique, kneading, fusion and solvent evaporation methods.[7,8,9] However, the solvent evaporation technique enables dispersion at the molecular level, improves wetting and allows the transformation of the crystalline constituents into their various amorphous states, which increases the surface area exposed to the surrounding dissolution medium.[10] One of the major components of the solid dispersion system is a hydrophilic polymer which acts as the drug carrier. Starch has been widely used in drug formulation. It is a major constituent of grains usually isolated from the endosperm of the kernel by the wet milling process.

Maize (Zea mays) is a major staple grown all over the world particularly Asia, Latin America and Africa. It is one of the most important grains worldwide second only to wheat and rice. It is widely referred to as the "cereal of the future" due to its high nutritional value and the diverse use of its by-products.[11] Agricultural research has focused on a large number of maize plant breeding programs to develop new genotypes or cultivars with improved qualities such as high starch and nutrient contents, improved yield, enhanced tolerance to drought, pest, weed competition, heat stress, cold temperature stress and herbicides. As part of these breeding programs, the International Institute of Tropical Agriculture (IITA) in Nigeria has produced a Pro-vitamin A-rich maize genotype (IWD 15). These genotypic modifications might improve the functionality of its starch in pharmaceutical dosage forms in which it is used as an excipient.[12] Most of the earlier works on cefixime solid dispersion utilized synthetic polymers as hydrophilic carriers.[13,14,15] The use of natural polymers, such as starch, is preferred because of their safety, biocompatibility and biodegradability.[16] The use of starch and blends of starch as hydrophilic carriers for cefixime solid dispersion has not been evaluated. The synergistic effect of the use of the blend of two hydrophilic polymers as carriers in solid dispersion has earlier been reported.[17] In this study, cefixime was formulated as solid dispersion using a blend of starch isolated from maize genotype and hydroxypropyl cellulose (HPC) to enhance its solubility and bioavailability. The morphology, thermal and spectroscopic characteristics of solid dispersion formulation with the highest solubility were measured using scanning electron microscopy, differential scanning spectroscopy and Fourier transform infra-red spectra studies respectively. The tablet properties of the optimum formulation were thereafter determined.

MATERIALS AND METHODS

Materials

The materials used include cefixime trihydrate (Zim Laboratories Ltd., Nagpur, India), hydroxypropyl cellulose-SL (Nippon Ltd, Tokyo, Japan), polyethylene glycol 6000 (Sigma-Aldrich Chemie GmbH, Germany) and genetically modified starch prepared at a laboratory in the Department of Pharmaceutics and Pharmaceutical Technology, Olabisi Onabanjo University, Nigeria. Maize grain genotype (IWD 15) was obtained from the International Institute of Tropical Agriculture (IITA), Nigeria. All other reagents used were of analytical grade.

Preparation of starch from maize genotype.

Starch was extracted from IWD 15 using an earlier reported method.[18] Grains of IWD 15 were washed with water to remove foreign materials. The washed grains were soaked in sodium metabisulphite solution (0.75 % w/v) for 24 h and crushed using a blender; the starch

dispersion was sieved using a calico cloth and left to stand at room temperature overnight. The supernatant was discarded and the sediment (starch) was washed with distilled water and then air-dried for 24 h. The dried starches obtained were pulverized in a mortar and coded as GM1.

Preparation of solid dispersion

The solvent evaporation method was used to prepare the solid dispersions. The required amount of cefixime, hydroxypropyl cellulose, genetically modified starch and polyethylene glycol (PEG 6000) (according to Table 1) were weighed into a mortar and triturated for 15 minutes until a fine blend was obtained. The blend was dissolved completely in 80 % w/w ethanol to obtain a transparent solution which was air dried for 24 hrs. The dried formulation was crushed in a mortar, sieved using a mesh size 60 and stored in an air-tight cellophane envelope.

Table 1: Composition (w/w) of cefixime solid dispersion formulations

	Formulations				
Ingredients (g)	P1	P2	P3	P4	P5
Drug	2.00	2.00	2.00	2.00	2.00
GM1	1.00	1.33	0.67	2.00	-
HPC	1.00	0.67	1.33	-	2.00
PEG 6000	0.50	0.50	0.50	0.50	0.50

GM1 - Starch isolated from genetically modified maize IWD 15; HPC- hydroxypropyl cellulose; PEG 6000- Polyethylene glycol MW 6000.

Determination of solubility

To determine the solubility of the solid dispersion formulation and plain cefixime, an excess amount was mixed with 1 mL of distilled water in a 2 mL microtube. The mixture was stirred with a vortex mixer for 1 minute and then agitated in a water bath for 5 days at 25°C and 100 rpm. It was then centrifuged at 5000 g and 0.5 mL of the supernatant was taken and properly diluted with ethanol. This diluted mixture was then analysed at 288 nm using a UV-visible spectrophotometer. Statistical significance was determined by comparing the data from the different formulations using one-way analysis of variance (ANOVA).

Scanning electron microscopy (SEM)

Solid dispersion formulation (P1), cefixime (A), starch isolated from maize genotype (GM1) and hydroxypropyl cellulose (HPC), physical mixtures of P1 (PM)were mounted on metal stubs, coated with gold and analyzed using the Scanning Electron Microscope (ZEISS EVO18, Germany). Image resolutions of the samples' surfaces were obtained at x 1000 magnification at a current of 7 mA for 90 s.

Fourier transform infra-red spectra studies (FT-IR)

The samples were triturated with potassium bromide, made into pellets (1 ton/cm2) and the infra-red (IR) spectra were obtained between scanning ranges of 4000 and 350 cm^{-1} using the (BX 273, Perkin-Elmer, USA). All the spectra were the average of 16 scans and were acquired at a resolution of 4 cm^{-1}.

Differential scanning calorimetry (DSC)

Cefixime powder, hydroxypropyl cellulose (HPC), starch isolated from maize genotype (GM1), the optimized formulation and a physical blend were analyzed using a differential scanning calorimeter (DSC1, Toledo, USA). The physical blend was obtained by weighing cefixime, HPC and GM1 starch in the same weight ratio as in the optimal formulations (P1) and mixing using a mortar and a pestle. The samples (5.5 mg) were placed in the aluminium pans of the equipment and scanned between 60 and 300^{o}C at a heating rate of 10^{o}C/min under inert nitrogen flow.

Powder X-ray diffraction (XRD)

The samples were exposed to an X-ray beam at 45 KV and 40 mA using an X-ray diffractometer (Empyrean, PAN

analytical, Netherlands). The scanning of the samples was done between 10^0 - 90^0 2*0* range with 0.10 resolution.

Preparation and evaluation of tablets

The solid dispersion blends (Table 2) were directly compressed into tablets using a hydraulic tablet press (Model C Carver Inc., USA) at a pressure of 1 tonne and a dwell time of 30 seconds. Before each compression cycle, the punches and die assembly were lubricated with a 2% magnesium stearate solution in 96% alcohol. The compressed tablets were kept in sealed envelopes before further analysis. The tablet friability was determined with a Roche (Erweka GmbH, Heusenstamm, Germany) friabilator operated at a speed of 25 rpm for 4 min while hardness was measured with a Monsanto hardness tester (Copley Scientific Limited, Nottingham, UK) using established procedures.[19]

Table 2: Composition of cefixime solid dispersion tablets

Constituent	Quantity (mg)
Solid dispersion	≈ 100 mg of cefixime
Microcrystalline cellulose	15
Magnesium stearate	2
Lactose to	300

***In vitro* release studies**

The dissolution studies were carried out using a Model NE4-COPD dissolution apparatus (Copley Scientific Limited, Nottingham, UK). The medium was a pH 7.4 phosphate buffer solution maintained at a temperature of 37 ± 0.5 ^{0}C. An amount of sample equivalent to 100 mg cefixime was added to 900 ml of the medium and the apparatus was operated at 100 rpm. At 5, 10, 15, 30, 45, and 60-minute intervals, a 5 mL sample was withdrawn and replaced with the same volume of fresh dissolution medium maintained at the same temperature to maintain sink conditions. The withdrawn samples were then filtered and the UV absorbance was measured at a wavelength of 288 nm on a UV-Vis spectrophotometer. The test was carried out in triplicates. The same procedure was repeated for the tablet formulation.

RESULTS

Solubility and dissolution

The solubility values of pure naproxen and naproxen solid dispersions are depicted in Figure 1.

Formulation P1 had the highest solubility of 15.2 ± 0.23 mg/mL which was almost twice more soluble than the other solid dispersions and three times more soluble than plain cefixime (5.0 ± 0.1 mg/mL). The data from the dissolution studies (Figure 2) showed that the time taken for 80 % drug dissolution from the solid dispersions was P1-50.0 mins; P2-48.8 mins; P3-41.8 mins; P4-48.9 mins; P5-61.2 mins and cefixime-45.9 mins. The rank order of dissolution rate of the solid dispersions was P3>cefixime>P2>P4>P1>P5. Although P2, P3 and P4 showed better dissolution than P1, their dissolution rate was not significantly different ($p>0.05$) from that of P1. Therefore, based on superior solubility and good dissolution profile, P1 was selected as the optimum formulation and further studies were carried out.

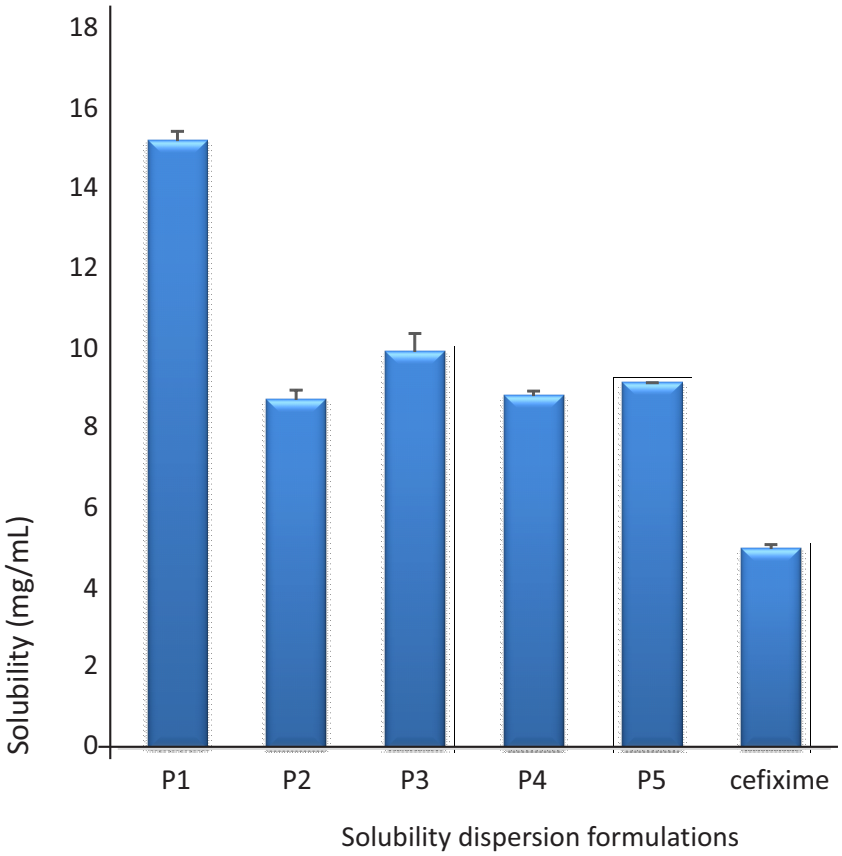

Fig. 1. Solubility of Cefixime solid dispersion formulations

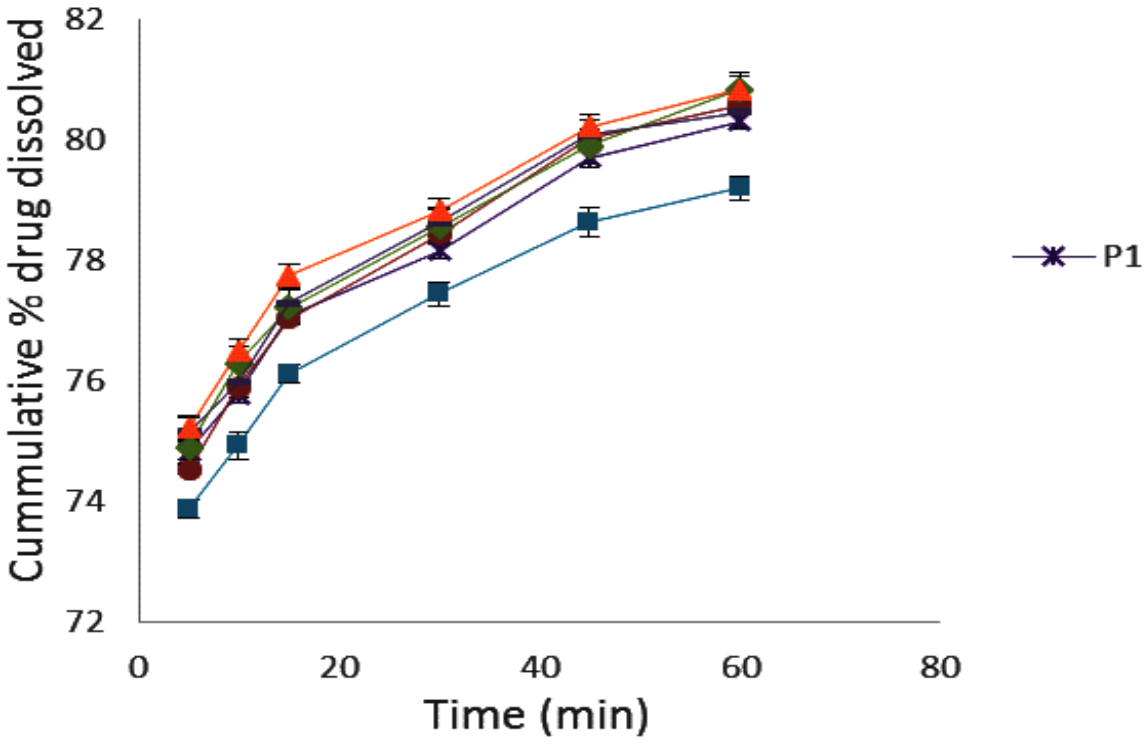

Fig. 2. Dissolution profile of Cefixime solid dispersion formulations

Morphology

The SEM micrographs presented in Figure 3 reveal that cefixime particles are irregularly shaped and of varying sizes. The genetically modified starch morphology is a blend of single and compound granules composed of 2-3 units while HPC appeared as interwoven coiled strands with a porous structure. The surface morphology of the solid dispersions revealed wide long fibrous strands with rough textured surfaces. The characteristic shapes of the individual constituents of the solid dispersion were not apparent in the morphology of the solid dispersion.

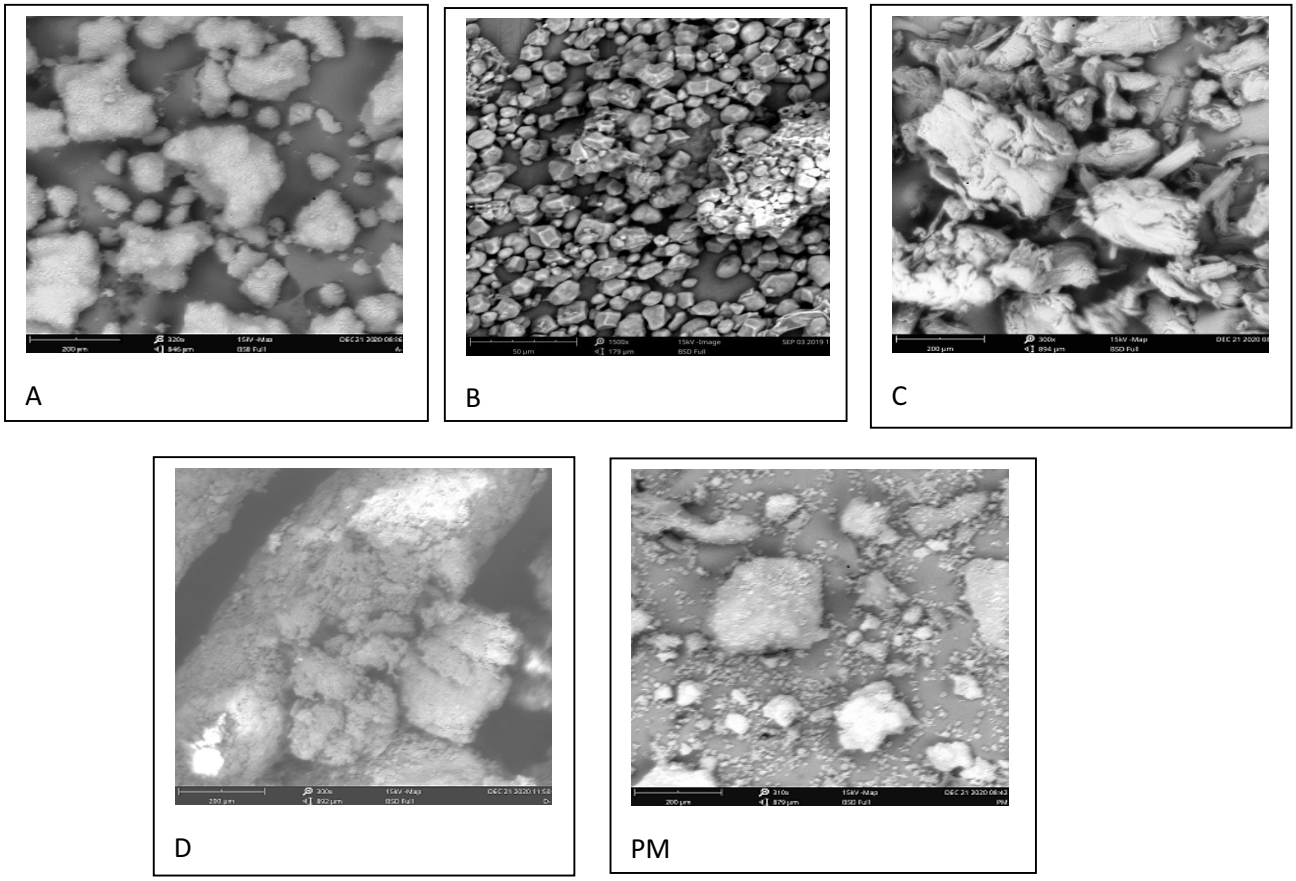

Fig. 3: Scanning electron micrograph (SEM): cefixime (A), genetically modified starch (B), HPC (C), solid dispersion P1 (D), physical mixture of P1 (PM)

Fourier transform infrared spectroscopy (FTIR)

The spectra of the samples are shown in Figure 4. The spectra of cefixime are characterized by distinctive peaks at 3283 cm^{-1} (N-H stretching mode), 2967 cm^{-1} (C-H stretching), 1666 cm^{-1} (C-O vibration), 1338 cm^{-1} (C-N mode) and 745.5 cm^{-1} (C-H bending) which is consistent with existing literature.[20] The spectrum of the physical mixture and the solid dispersion are similar with identical peaks. The spectrum of HPC was characterized by broad peaks at 3429 cm^{-1} (O-H stretching), a C-H peak at 2970 cm^{-1} and a C-C stretching mode at 1660 cm^{-1} while the spectrum of starch from the maize genotype had broad round peaks at 1640 cm^{-1} (due to tightly bonded water molecules) and 2928 cm^{-1} (stretching mode of the amylose and amylopectin content).[12]

Thermal Properties

The DSC thermograms of the samples are presented in Figure 5. The result shows multiple sharp endothermic peaks at 64 °C and 113 °C or cefixime and physical mixtures of P1. No exothermic peak was observed for the solid dispersion. Table 3 shows the gelatinization temperatures, gelatinization temperature range and the enthalpy of gelatinization. There was a decrease in T_o, T_p and T_e of the SD compared to the plain cefixime. The highest value of enthalpy of gelatinization was observed for cefixime.

Table 3: Thermal properties of excipients and solid dispersion formulations

Sample	Gelatinization temperatures			ΔT(Te- To)	ΔH (J/g)
	To (^{0}C)	Tp (^{0}C)	Te (^{0}C)		
A	30.79	80.25	124.27	93.48	109.21
B	31.21	54.47	105.15	73.94	52.83
C	31.17	43.02	117.95	86.78	82.35
D	30.00	64.11	122.12	92.12	89.90
PM	90.13	110.65	121.50	31.37	0.92

A-cefixime, B- genetically modified starch, C- HPC, D- solid dispersion P1, PM- physical mixture of P1, H, gelatinization enthalpy; Tp, peak temperature; Te, Endset temperature; To, onset temperature; T, gelatinisation temperature range

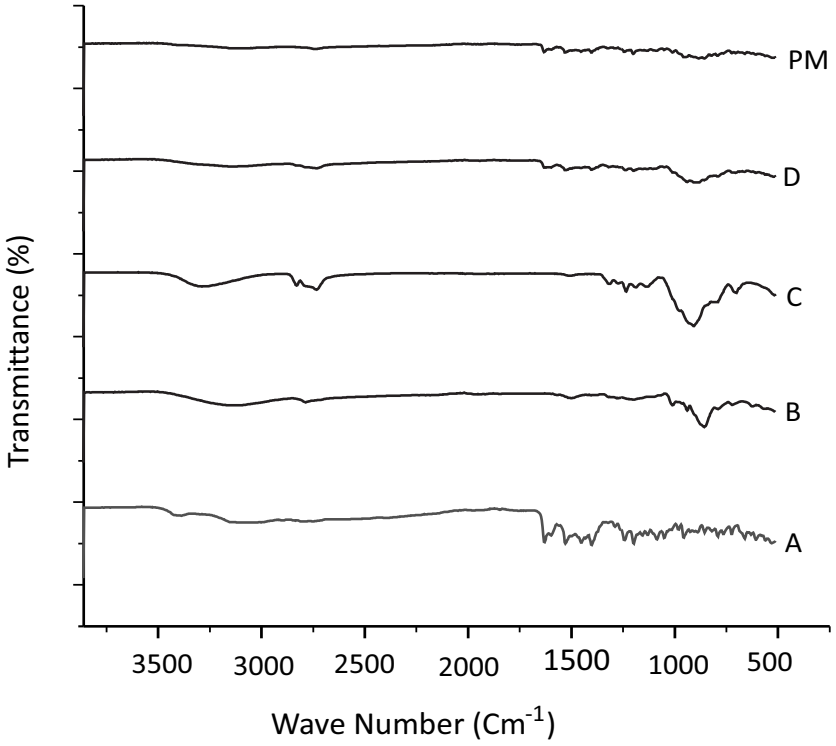

Fig. 4. Fourier-transform infrared spectroscopy (FTIR) spectra: cefixime (A), genetically modified starch (B), HPC (C), solid dispersion P1(D), physical mixture of P1(PM)

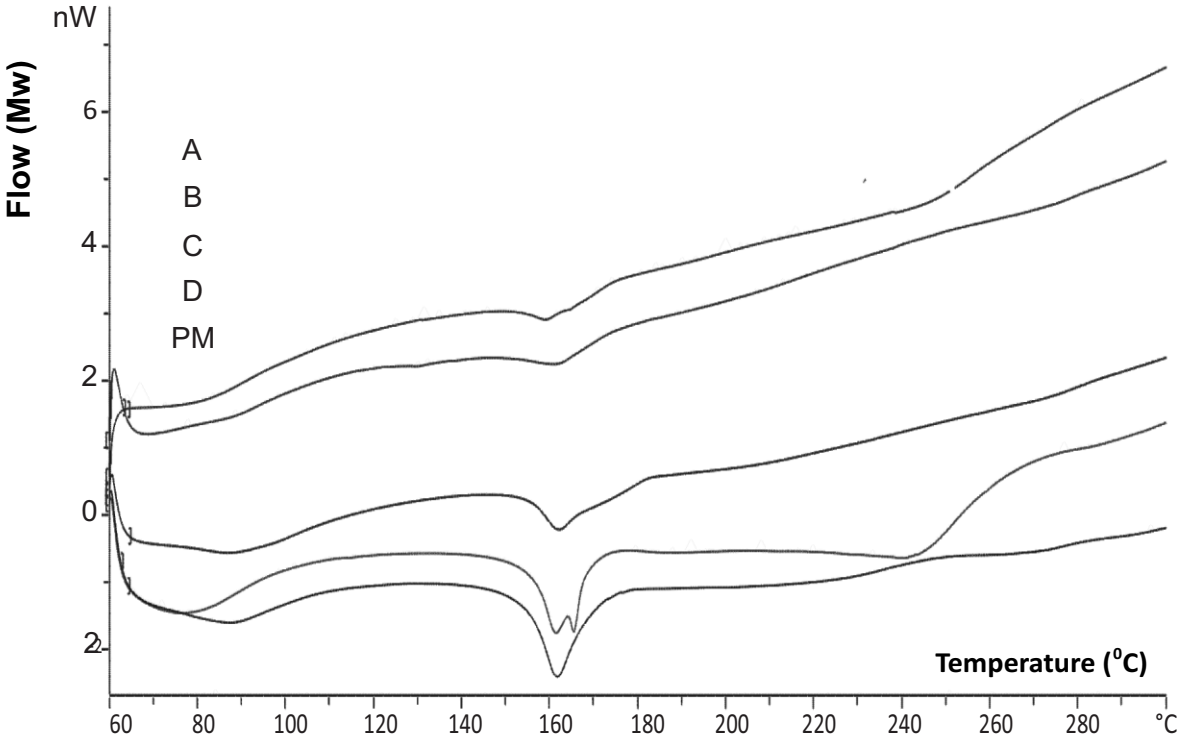

Fig. 5. Differential scanning calorimetry thermograms: cefixime (A), genetically modified starch (B), HPC (C), solid dispersion P1 (D), physical mixture of P1 (PM)

X-ray diffraction

The XRD spectra of the samples (Figure 6) showed that the genetically modified starch has a broad peak with a region between 10 and 30°. The presence of both broad and sharp peaks was observed in the cefixime diffractogram. The X-ray pattern of the solid dispersion formulation is not well resolved. It is characterized by broad humped peaks with low intensity and a noisy pattern.

Solid dispersion tablet

Table 4 shows the properties of the solid dispersion tablets. The solid dispersion formed hard and friable tablets. The time taken for 50 % and 90 % of the drug to be released (Figure 7) was higher than that of tablets containing plain cefixime.

Table 4: Mechanical and release properties of tablet formulation

Formulations	Hardness (N)	Friability (%)	T_{50} (min)	T_{90} (min)
A1	148.0 ± 0.06	4.0	37.6	75.8
AC	39.2 ± 0.04	20.8	18.2	50.0

A1 contains solid dispersion P1, AC contains plain cefixime

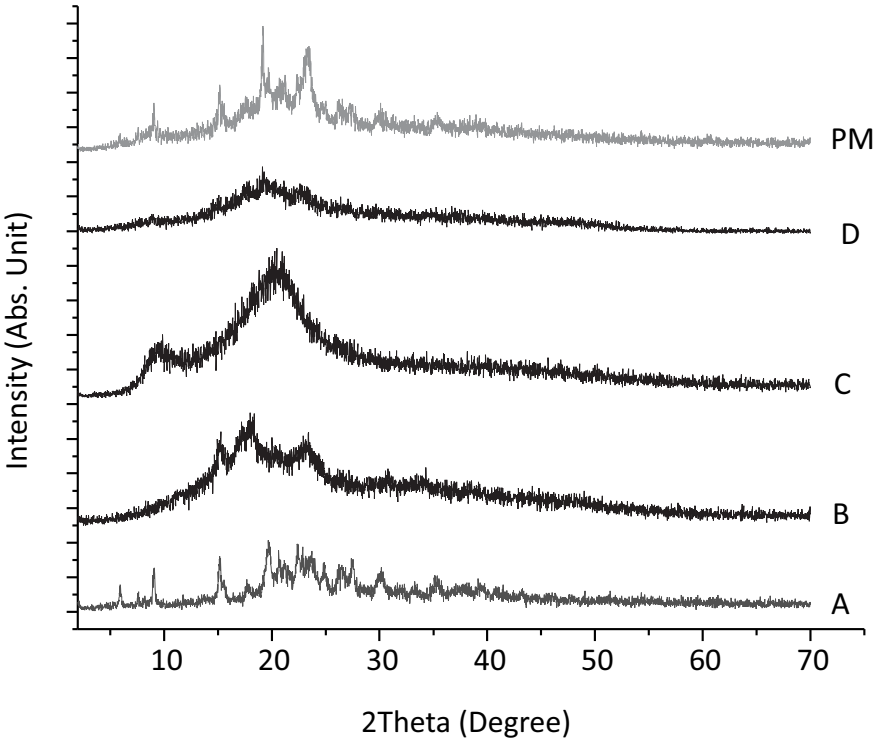

Fig. 6. X-ray diffraction pattern: cefixime (A), genetically modified starch (B), HPC (C), solid dispersion P1 (D), physical mixture of P1 (PM)

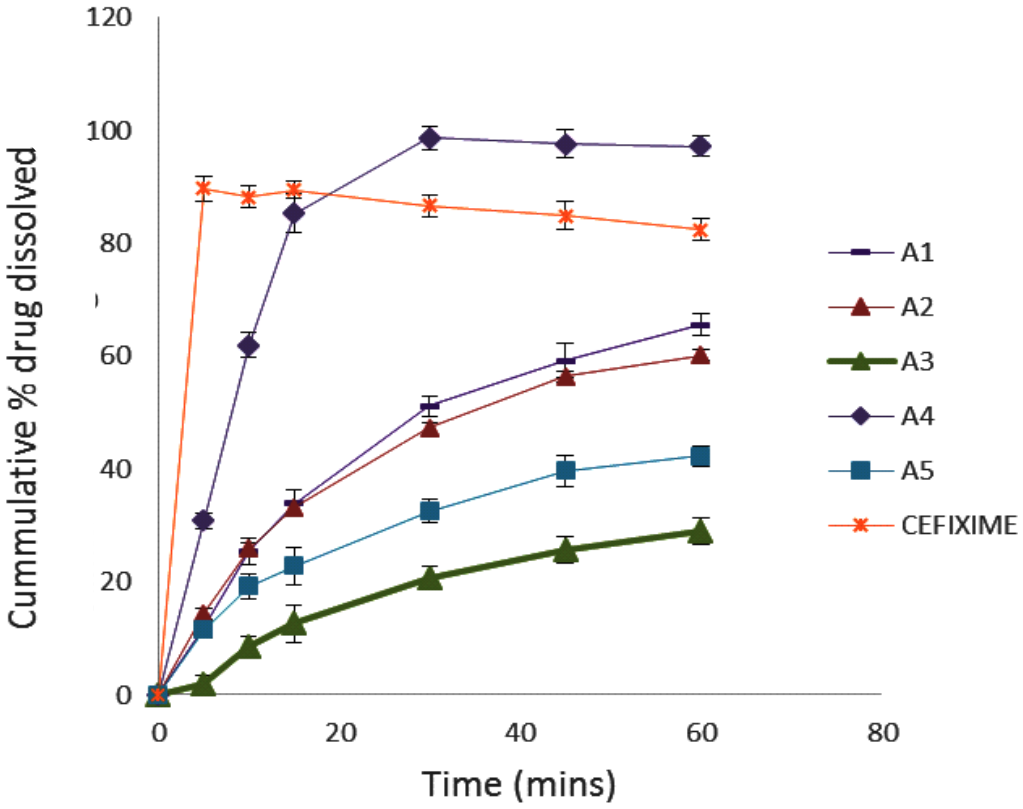

Fig. 7. Dissolution profile of solid dispersion tablet formulations and pure cefixime

DISCUSSION

All the solid dispersion formulations were more soluble than the plain drug. The improved solubility is probably due to the amorphization of the drug. The cefixime solid dispersions belong to the second-generation solid dispersion because they contain starch, an amorphous carrier.[21] Amorphous carriers enhance the dispersibility and wettability of the drug and also prevent drug precipitation when the formulation is dissolved in water. In addition, the presence of PEG which has a high water solubility could also have contributed to enhanced wetting of the drug. It was observed that the formulation containing the blend of HPC and genetically modified starch at a 1:1 ratio showed higher solubility than those having individual polymers. This suggests the combination exhibited a synergistic effect. This is similar to the report of Pöstges *et al*.[17]

The micrographs also reveal that the individual morphology of cefixime, HPC and the starch from maize genotype seem to disappear with the formation of the solid dispersion which has a distinct morphology. This could be due to the molecular dispersion of cefixime into the hydrophilic polymer matrix in an amorphous form which resulted in its loss of crystallinity as confirmed by the XRD diffractogram.[22] The complete change in morphology is also an indication that the cefixime was well incorporated into the starch and HPC blend, which will prevent the recrystallization of the drug.

The presence of the major characteristic peaks from the constituents of the solid dispersion at about the same wavelengths as found in the individual components suggested that there was no significant interaction between the drug and the polymers. Even though the physical mixture and the solid dispersion had identical peaks, those of the solid dispersion appeared at slightly lower wavelengths compared to the physical mixtures. This indicates that weak bonds were formed in the solid dispersion formulation. The bands at 1666 and 1592 cm^{-1} shifted to a lower wavelength of 1651 and 1586 cm^{-1} respectively in the solid dispersion. This suggests the presence of hydrogen bonding in the crystalline drug but the bonding was spread out in the solid dispersion. The C-O vibration in cefixime probably interacted with OH functional groups in the HPC at the molecular level in the solid dispersion which stabilizes cefixime in the higher energy amorphous state and prevents crystallization.[23] The spectrum of HPC was characterized by broad peaks at 3429 cm^{-1} (O-H stretching), a C-H peak at 2970 cm^{-1} and a C-C stretching mode at 1660 cm^{-1} while the spectrum of starch from the maize genotype had broad round peaks at 1640 cm^{-1} (due to tightly bonded water molecules) and 2928 cm^{-1} (stretching mode of the amylose and amylopectin content).[12]

The first endothermic peak observed in the DSC thermogram may be attributed to the gelatinization of the starch while the second peak is due to the melting of the complex formed by amylose and the lipid impurities in the genetically modified starch.[24] There was no exothermic peak observed for solid dispersion probably because crystallization did not occur. The highest value of enthalpy of gelatinization, H observed for cefixime suggests a large amount of intramolecular bond within the drug. A reduction in H was observed when cefixime was made into solid dispersion. This is likely to be due to a reduction in the rigidity of the cefixime structure following the formation of solid dispersion. This resulted in a decrease in the energy needed to disrupt its structure.

In the XRD diffractogram, the broadness observed between 10 and 30^0 for the genetically modified is suggestive of its amorphous nature. The presence of broad and sharp peaks in the cefixime spectra is an indication of the presence of both amorphous and crystalline structures. The absence of the observed cefixime characteristic sharp peaks in the solid dispersion diffractogram is an indication of the transformation of the drug into an amorphous material. This is consistent with the result of the DSC. The physical mixture retained the sharp crystalline peaks associated with cefixime which is an indication that the drug remained in its semi-crystalline state. It is suggested that the formulation of the solid dispersion using the hydrophilic polymers achieved the amorphorization of cefixime which the physical mixture could not.

Tablet hardness has been reported to impact release properties hence it is used routinely as a quality control assessment parameter. In addition, conventional compressed tablets that lose less than 1.0 % of their weight during friability testing are generally considered acceptable.[25] It has been reported that the hardness of a tablet depends on the bonding strength between particles and the strength of the inter-particulate bonds formed during compaction can be affected by the brittleness/elasticity of the material, and the rate of tablet compression.[26] The solid dispersions exist as wide long fibrous strands with rough textured surfaces which might have undergone deformation to fill gaps between the particles resulting in stronger bonds and a high hardness

value. The time taken for 50 % and 90 % of the drug to be released (Figure 7) was higher than that of tablets containing plain cefixime. The solid dispersion had a steadier release pattern, compared to the cefixime tablet which suggests that solid dispersion may be suitable for sustained release of cefixime.

CONCLUSIONS

The optimum formulation was three times more soluble than the plain cefixime and also showed an acceptable dissolution profile. The individual morphology of the components of the solid dispersion was lost with the formation of the solid dispersion. The FTIR peaks appeared at slightly lower wavelengths in the solid dispersion compared to the physical mixtures which indicates that weak bonds were formed in the solid dispersion formulation. XRD spectra of the solid dispersion revealed that the drug was transformed into a highly amorphous material. Therefore, the solid dispersion technique using starch from maize genotype as polymer provides a means to improve cefixime solubility and may sustain its release in tablet formulation.

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