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Formulation and Evaluation of Oral Dissolving Films of Amlodipine Besylate Using Blends of Starches With 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 the article

Abstract

Background. Natural polymers serve as cheap, non-toxic, biocompatible excipients in oral drug delivery. These advantages inform their uses in the design of drug dosage forms.

Objectives. The aim of the study was to prepare and evaluate oral dissolving films of amlodipine besylate, an anti-hypertensive drug, using starch/polymer blends.

Material and Methods. Bambara nut (BAM) and the African yam bean (AYB) starches were individually blended with hydroxypropyl methyl cellulose (HPMC). The material and rheological properties of the blends were determined. Amlodipine besylate was incorporated by dispersion and films were prepared by solvent evaporation method and evaluated for mechanical and drug release properties.

Results. The BAM/HPMC blends had higher viscosity values than the corresponding AYB/HPMC blends. All the blends gave a Hausner ratio above 1.25 and Carr's index above 22. Blends of ratio 1 : 1 and 2 : 1 produced good films and were subsequently evaluated. All films disintegrated within 15 mins but had poor folding endurance. BAM/HPMC (1 : 1) and AYB/HPMC (2 : 1) released all of the drug content within 30 min. The ranking for dissolution profile was AYB/HPMC (2 : 1) > BAM/HPMC (1 : 1) > BAM/HPMC (2 : 1) > AYB/HPMC (1 : 1). The type and ratio of starch in the blend influenced the drug release pattern of the films.

Conclusions. Starch/HPMC blend ratios of 1 : 1 and 2 : 1 were found suitable for the formulation of oral dissolving film of amlodipine besylate with good disintegration time and drug release profile (**Polim. Med.** 2016, 46, 1, 45–51).

Key words: African yam bean starch, Bambara nut starch, oral films, HPMC blends, amlodipine besylate.

The oral route remains the most widely accepted route of drug administration due to the numerous merits offered over other routes [1]. This route of administration is non-invasive, requires no special training, toxicities and over-dosage can be easily managed. However, what is a major disadvantage, especially in children and elderly patients, is difficulty in swallowing tablets and capsules.

The emergence of oral dissolving films alleviates the drawback of swallowing difficulties and fear of choking associated with tablets, capsules and oral disintegrating tablets respectively, especially in pediatrics and geriatrics. The films are ultra-thin formulations of postage stamp size and contain active ingredients and excipi-

ents [2]. They are usually administered by the sublingual or buccal routes [3]. Films deliver a measured dose of a drug to the site of administration and thereby offer an advantage over creams and ointments [4].

Amlodipine is a dihydropyridine calcium channel blocker used in the management of hypertension and angina pectoris. It is long-acting with effects similar to nifedipine [5]. Administered orally, the drug is well absorbed and peak blood concentration is reached after 6–12 h. Plasma elimination is biphasic and terminal elimination half-life is about 30–50 h. Absolute bioavailability of between 60 and 65% has been estimated [6].

There are published reports on oral dissolving films of amlodipine besylate using synthetic polymers [7–10].

However, the association of these synthetic polymers with mucosal irritation proved a limitation [11]. Natural polymers have advantages of local accessibility, eco-friendliness, biodegradability, renewable source and low price [12]. This work, therefore, aims at investigating the use of locally sourced starches in formulating oral films of amlodipine besylate. The chemical structure of amlodipine besylate is shown in Fig. 1.

Starch, which is inexpensive and fully biodegradable, has been extensively studied for many years in the field of materials [13–15]. Generally, starches are abundant, non-toxic and biocompatible [16]. Starch films are transparent or translucent, flavorless and without color and taste [17]. The application of starch film is, however, limited by both poor mechanical strength and an efficient barrier against low polarity compounds.

Hydroxypropylmethyl cellulose (HPMC) has been used as a standard polymer. It is a chemically modified polymer prepared from alkali treated cellulose that reacts with methyl chloride and propylene oxide. It has a reversible thermal gelation property and forms hydrophilic matrices which mainly act by way of diffusion-controlled drug release [18]. Its hydrophilic nature informed our choice. The chemical structures of both amlodipine besylate and HPMC are shown in Figures 1–2 respectively.

The aim of this work was to formulate and evaluate oral dissolving films of amlodipine besylate prepared from physical blends of Bambara nut and African yam bean starches with HPMC.

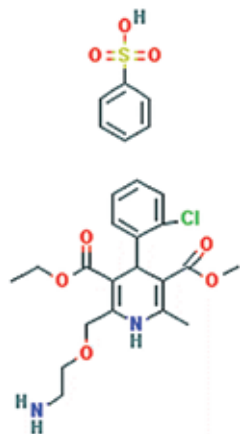


Fig. 1. Chemical structure of amlodipine besylate

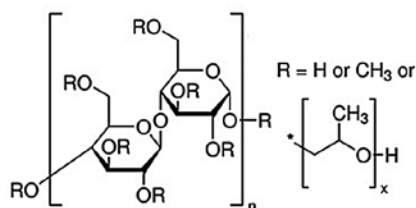


Fig. 2. Chemical structure of hydroxypropylmethyl cellulose (HPMC)

The novelty of the work is in the use of new polymers obtained from bambara nut and African yam bean; the work investigated these two new starches in formulating the amlodipine besylate films. The starches were blended with an established polymer, HPMC, and were found to have good film forming properties and good drug release characteristics.

Materials and Methods

Materials

Bambara groundnut (purchased locally at Bodija market, Ibadan, Nigeria), African yam bean (purchased locally at Bodija market, Ibadan, Nigeria). Bambara groundnut and African yam bean are readily available in any local market in the South West of Nigeria. Hydroxypropyl methyl cellulose (HPMC) 5Mpa, Amlodipine besylate powder (Impact Lab Pvt. Ltd, Mumbai, India), disodium hydrogen orthophosphate (Hopkins & Williams, England), potassium dihydrogen phosphate (Lab Tech Chemicals), sodium dihydrogen orthophosphate (BDH Chemicals Ltd.), glycerol (BDH chemicals Ltd, England).

Methods

Starch Extraction

Bambara and African yam beans were thoroughly washed separately and soaked in water for 48 h. The beans were then milled and later sieved through a muslin cloth. The filtrate was allowed to stand for 24 h. Water was decanted off the settled residue and the residue washed two times daily over a period of 4 days. The remaining residue was then oven-dried at 50°C for 48 h. The dried starches were pulverized, kept in airtight containers and used for further investigations.

Particle Size and Surface Morphology

The particle size and surface morphology of each starch were respectively determined, using optical microscope (MT3300EXXII, Microtrac Bel, Japan) and Scanning Electron Microscope (Model S3400N, Hitachi, Japan). Scanning of the surface was carried out and photomicrographs taken at 20Kv voltage.

Blending of Starches and HPMC

Four ratios each of Bambara and African yam bean to HPMC (1:1, 2:1, 4:1 and 5:1) were prepared. A fraction of the starch was each time placed in a mortar and similar amount of HPMC added. These were thoroughly mixed over 5 min with the aid of a pestle. The remaining parts were gradually added and mixed until a homogenous blend was achieved.

Swelling index

Quantities, 5 gm, of the starches and starch/HPMC blend of four ratios were weighed and placed into different measuring cylinders. The occupied volumes in each cylinder were determined after which 90 mL of distilled water was added. The mixture was shaken for five minutes after which the volume was made up to 100 mL. The cylinders were left on the shelf for 24 h and the volume of the sediments measured thereafter. The swelling index was estimated as the ratio of the initial volume to the sediment volume after 24 h. Measurements were made in triplicates.

Hausner Ratio

Quantities (30 g each) of the starches and starch/HPMC blends were put in graduated cylinder. 100 taps were applied at 38 taps per minute to obtain a tapped volume. The Hausner ratio was the ratio of the initial bulk volume to the tapped volume.

Carr's Index

This was calculated by applying the equation:

$$\frac{(\text{Tapped density} - \text{Bulk density}) \times 100}{\text{Tapped density}} \quad (1)$$

Viscosity

The viscosity of the starches and starch/HPMC blends at 10%w/v concentration were determined at room temperature using a viscometer (Brookfield Model DV-11 + Pro viscometer).

pH Determination

The pH of 10% dispersion of starch and starch/HPMC blends in water was determined using a pH meter.

Film Preparation

Solvent evaporation technique was employed to formulate the films. 10%w/v mixture of the starches and starch/HPMC blends in distilled water were prepared. Quantity, 20 mg of amlodipine besylate was dispersed in 20 mL of the mixture and 1%v/v of glycerol added as plasticizer. This was poured in a plastic petri dish and allowed to stand until all bubbles disappear.

The petri dish was placed in an oven at 50°C for 2 h. The films are subsequently removed from the dish and cut into pieces. Films that could not be removed from the dish were judged to have failed.

Films were made from Bambara starch, African yam bean starch as well as blends of Bambara/HPMC and African yam bean/HPMC. Four ratios of starch/HPMC were prepared. These ratios are 1:1, 2:1, 4:1 and 5:1. The best-formed films were selected from the multitude.

Visual Inspection

The prepared films were visually observed for color, transparency and homogeneity to assess some organoleptic properties.

Weight Variation

Films $2 \times 3 \text{ cm}^2$ in size were weighed on an electronic balance. The measurements were carried out in triplicates.

Folding Endurance

This gives an indication of the brittleness of the film. The film was repeatedly folded in the same spot until it broke. The folding endurance was taken as a function of the number of times the film is folded before breakage.

Film Thickness

The measurement of the thickness of each film was determined using a micrometer screw gauge. Measurements were taken at five different spots (four corners and center) of the film. The measurements were taken in duplicates.

pH of Films

The film was wetted with distilled water, of a neutral pH and the electrode kept in contact with the surface. The pH was read on the pH meter and compared with the pH obtained for the plain polymers. This was carried out to determine the pH sensitivity of the polymers.

Disintegration Time

A 2 mL volume of distilled water was placed at the center of a petri dish. A $1 \times 1 \text{ cm}^2$ film was placed on the water. The time taken for the film to completely disintegrate into particles was taken as the disintegration time [19].

Drug Release

Dissolution was carried out using a Copley DIS 6000 tablet dissolution apparatus. Phosphate buffer (pH 6.8) was used as the dissolution medium to simulate the alkaline pH of the intestine. A film of $2 \times 3 \text{ cm}^2$ size was put in the basket and lowered into the dissolution flask containing 900 mL of the medium. The analysis was carried out at $37 \pm 2^\circ\text{C}$ and agitated at 50 rpm. Samples (5 mL) were taken every five minutes over a 30-min period. The withdrawn sample was replaced each time with another 5 mL of fresh dissolution medium and sink condition was maintained throughout the test. The absorbance of the withdrawn samples was subsequently measured at 239 nm by a Spectrumlab 752 s UV-Vis spectrophotometer. The drug content was estimated using standard curve of drug.

Statistical Analysis

The results obtained were subjected to statistical analysis using ANOVA, followed by a posthoc Tukey's test, where more than two sets of data were obtained, to determine the level of significance (p-value) of an effect or the difference between means. Parameters that are significant at 95% confidence were considered significant or different at $p = 0.05$.

Results and Discussion

Films prepared from AYB/HPMC blends were cream colored while those from BAM/HPMC were white in color. The surface morphology revealed smooth and non-transparent particles which are cylindrical to semi-spherical in shape with little aggregation (Fig. 3–6).

Properties of the starches and starch/HPMC blends are presented in Table 1. The physicochemical parameters

of the film are presented in Table 2. The respective drug release profiles of amlodipine besylate from the films are shown in Figure 7.

Surface morphology and particle size determination by Scanning Electron Microscopy and optical microscopy respectively showed starch particles of varying average sizes. Average particle size of BAM was 210 μm while AYB had the size of 300 μm . Similarities were observed in the shapes of particles of the two starch-

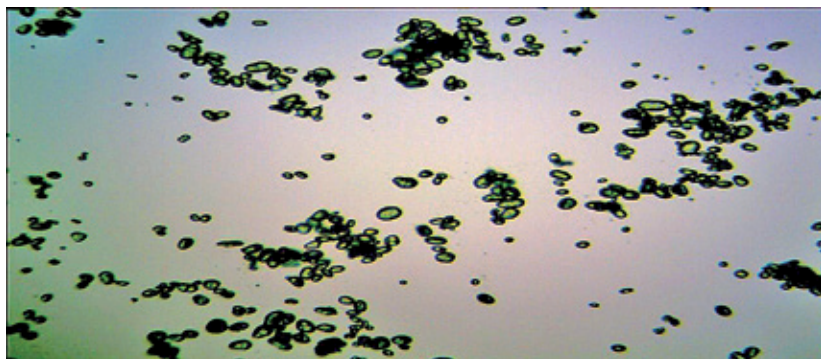


Fig. 3. SEM Photomicrograph of AYB Starch

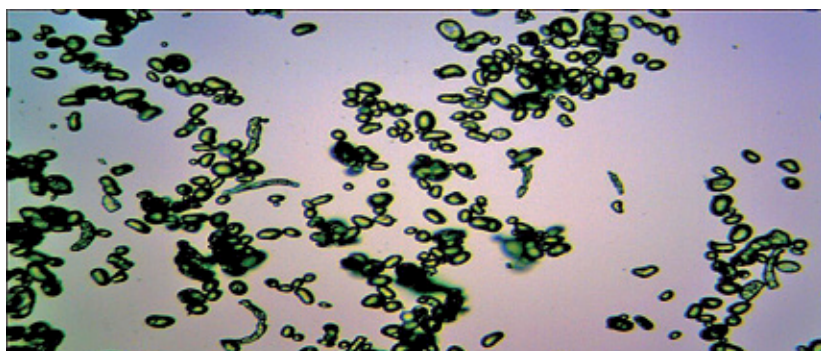


Fig. 4. SEM Photomicrograph of AYB/HPMC at Ratio 2 : 1

Table 1. Properties of the starch and starch/HPMC blends

Sample	Bulk density (g/cm ³)	Tapped density (g/cm ³)	Hausner ratio	Carr's index (%)	Viscosity (100 rpm)	Swelling index	Water absorption capacity	pH
AYB	0.61	0.88	1.44	30.68	10.0	0.92	26.0	7.35
AYB:HPMC (1 : 1)	0.60	0.77	1.28	22.08	48.0	0.67	77.0	7.24
AYB:HPMC (2 : 1)	0.60	0.83	1.39	27.71	26.0	1.08	77.0	7.43
BAM	0.46	0.83	1.83	44.58	10.0	0.91	84.0	6.75
BAM:HPMC (1 : 1)	0.38	0.73	1.93	47.95	54.0	0.75	88.0	6.95
BAM:HPMC (2 : 1)	0.47	0.77	1.64	38.96	35.0	1.19	87.0	7.16

Table 2. Properties of the oral films of Amlodipine besylate

Film	Thickness (μm)	Variation of mass (mg)	Disintegration time (sec)	Folding endurance	Surface pH
AYB:HPMC (1 : 1)	44.2 \pm 10.56	183.83 \pm 20.56	12.63 \pm 1.94	1.0 \pm 1.5	5.35
AYB:HPMC (2 : 1)	43.4 \pm 8.22	192.50 \pm 13.34	10.86 \pm 3.38	2.0 \pm 1.0	5.79
BAM:HPMC (1 : 1)	46.4 \pm 11.43	185.17 \pm 30.47	14.70 \pm 1.22	2.0 \pm 2.0	5.60
BAM:HPMC (2 : 1)	43.0 \pm 8.98	205.67 \pm 17.73	11.81 \pm 1.66	7.0 \pm 2.0	5.75

The Table shows the results of properties of Amlodipine films formulated with AYP and HPMC in the ratios 1 : 1 and 2 : 1.

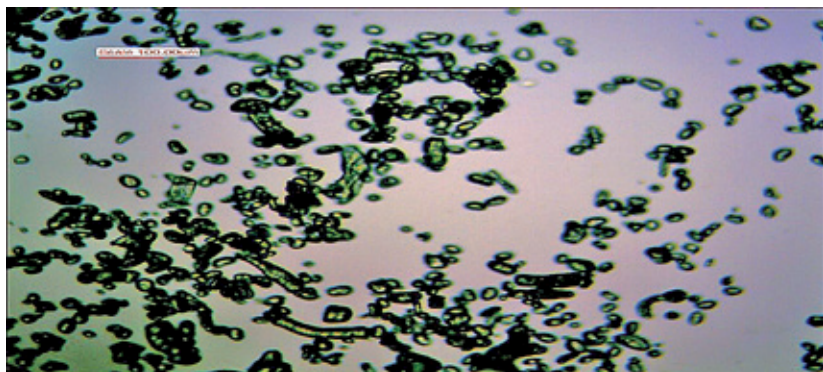


Fig. 5. SEM Photomicrograph of BAM/HPMC at Ratio 2 : 1

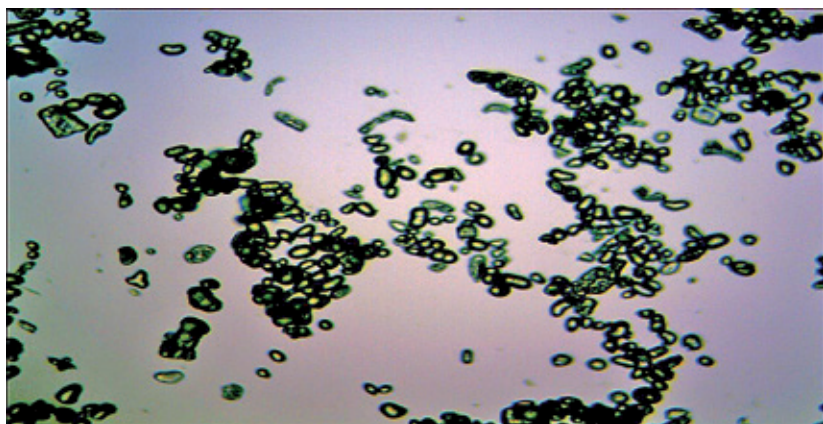


Fig. 6. SEM Photomicrograph of BAM Starch

es (Fig. 3–6); they had smooth surfaces, cylindrical to almost spherical in shape, with few aggregations. Fast dissolving dosage forms are expected to rapidly disintegrate and dissolve upon contact with the oral cavity; hence, the small particle size of these starches would allow rapid penetration of saliva fluid due to the large surface area and an increased area-to-volume ratio that limit the distance the fluid travels before reaching the center of the particles [20].

Values for the swelling index of the starch and starch/HPMC blends are shown in Table 1. The swelling index indicates the amount of liquid a material can absorb. The starches, as well as the starch/HPMC blends, had a low swelling index. The extent of swelling in polymers is a competition between two forces: the free energy of mixing, which makes the solvent penetrate in an attempt to dilute the polymer solution and the elastic retractile force which opposes the deformation. Swelling is said to be at a steady state when these two forces balance each other out [21]. The results suggest that the polymers reach a steady swelling state in a short time.

The polymers were observed to be basic with a pH range between 6.75 and 7.43 (Table 1). The surface pH of films also showed alkaline pH. This indicates that the polymers are not pH sensitive and are neither altering the pH of the drug nor affected by the pH of the drug.

The values of viscosity of 10%w/v starch and starch/HPMC blends as taken on a Brookfield DV-II+ Pro viscometer at 25°C are shown in Table 1.

The two starches, AYB and BAM, have similar viscosity values. This indicates that they have an identical amylopectin content. It has been reported that the amylose content of starch determines the gel strength, while viscosity is a function of the amylopectin content [22].

The ratio 1 : 1 of the starch/HPMC blends for both AYB and BAM had the highest viscosity values. These values decreased as the ratio proportion of starch increased in the blend. Overall, the BAM/HPMC blends had higher viscosity values than the AYB/HPMC.

Bulk and tapped densities can be used to determine the Hausner ratio and Carr's index. These are indications of flowability and compressibility of a powder. Free flowing powders have a lower Carr's index, while poor flowing have a higher Carr's index.

Carr's index values of below 15 signify good flowability and values above 25 indicate poor flowability. Also values of Hausner ratio above 1.25 indicate poor flowability [23].

The values shown in Table 1 indicate that the starch powders as well as the starch/HPMC blends have poor flowability. The AYB/HPMC blend of a 1 : 1 ratio had the least value for the Hausner ratio and Carr's index, which points to the fact that this ratio has the best relative flowability compared to others. This is followed by the 2 : 1 ratio. It was observed that both parameters decreased in both 1 : 1 and 2 : 1 starch blends. This flowability decreased with the increased amount of starch in the blend. This decrease and consequent increase in flowability may be attributed to the free flow-

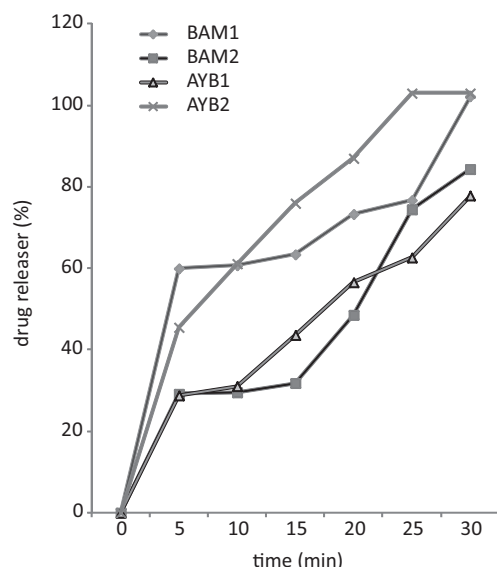


Fig. 7. Dissolution profile of amlodipine besylate films from starch/HPMC blends

ing HPMC. The result suggests that HPMC improved the flow property of the blends and that improving powder flow could be a means to producing good quality films with acceptable folding endurance. HPMC probably increased the plasticity of the blends and, hence, the rheological properties of the films improved. BAM and BAM/HPMC blends have poorer flowability than AYB and AYB/HPMC blends. This may be due to factors such as particle shape, particle size, intra and interparticulate interaction between the powders [23].

Bambara and African yam bean starches were used to formulate films. Also, blends of each starch with HPMC in the 1 : 1, 2 : 1, 4 : 1 and 5 : 1 ratios were used. Only films from starch/HPMC blends in the 1 : 1 and 2 : 1 ratios were of good quality. This result suggests that the starches alone have poor film forming properties but demonstrated good properties when blended with HPMC in appropriate ratios. Furthermore, results demonstrated that optimum starch concentration is needed in the blends for good film to be produced; above this optimum concentration, brittle starches with poor folding endurance were formed, despite the inclusion of glycerol, a plasticizer, in the formulation. However, formulations containing BAM had better folding endurance.

HPMC has a high glass transition temperature and this could be responsible for the brittleness observed in the films. Brittleness is a disadvantage in oral film dosage form as this will confer unnecessary fragility on the film. This will in turn make handling difficult.

The results for film thickness are presented in Table 2. The thickness ranged from 43.0 to 46.4 μm . Bambara starch produced films of higher thickness than AYB. The films' thickness appears ideal and suitable

for oral administration; film dosage forms must be easy to handle as the films are applied to the mouth one after the other [24]. The films had adequate strength to withstand handling during usage.

The disintegration time of the films ranged from 10.86 to 14.70 s (Table 2). BAM2 had the lowest while BAM1 had the highest disintegration time. Disintegration time for films is a function of the composition of the film formulation. A range of 5 to 30 s is termed to be appropriate [25].

The dissolution of a drug from the dosage form is one of the important parameters that determine bioavailability of that drug. The dissolution profiles of the films are shown in Fig. 7. There was 100% drug release from BAM1 and AYB2 within 30 min while 78 and 80% release was obtained from AYB1 and BAM2 respectively. Results of the *in vitro* drug release show excellent but slightly different profiles among the blends and starch concentrations; this is evident from the rapid and complete disintegration observed from the film formulations. Complete disintegration imparted increased surface area and penetration of the dissolving fluid because of the increase in area-to-volume ratio of the particles [20], thereby enhancing excellent dissolution profile. Bambara groundnut would give a complete drug release when used at a ratio of 1 : 1 with HPMC, whereas the African yam bean would give ultimate drug release at a ratio of 2 : 1. This clearly shows that individual physicochemical properties of the starches come into play in affecting drug dissolution from films. Increasing starch concentration improved drug release with African yam bean starch, while drug release decreased with increasing starch concentration with Bambara starch. It was also noted that the extent of the increase and decrease in the drug release profile of the starches was almost the same (80 to 100%). It is, therefore, possible to obtain complete drug release from the two starches, depending on the concentration used.

A plateau in the release profiles was observed for BAM1 and BAM2 at 5 to 15 min; this plateau period could be due to the swelling phase of the formulation, during which there was a steady release of the drug. However, this constant release was not observed in AYB formulations; this further shows that properties of the individual starch in the blends affect release of drug from the films.

The African yam bean and Bambara nut starches were blended with HPMC in different ratios, ratios 1 : 1 and 2 : 1 produced acceptable amlodipine oral dissolving films with good release profile. Furthermore, HPMC improved the flow properties of the starches and it led to production of good quality films at optimum concentrations. Native starches, being readily available and cheap, can be blended with synthetic polymers at appropriate proportions to reduce production cost.

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Conflict of interest: None declared

Received: 29.04.2016

Revised: 18.08.2016

Accepted: 7.09.2016