Freeze-dried pregelatinized *Dioscorea* starches as tablet matrix for sustained release.

Oluwatoyin A. Odeku[a,b], Katharina M. Picker-Freyer[a*]

[a]Institute of Pharmacy, Div. of Pharmaceutics and Biopharmaceutics, Martin-Luther-University Halle-Wittenberg, Wolfgang-Langenbeck-Strasse 4, 06120 Halle/Saale, Germany
[b]Faculty of Pharmacy, Department of Pharmaceutics and Industrial Pharmacy, University of Ibadan, Ibadan, Nigeria.

Received: 3 May 2010; Accepted: 18 July 2010

ABSTRACT

Two freeze dried pregelatinized *Dioscorea* starches have been evaluated as directly compressible excipients for sustained release using diclofenac sodium and caffeine as the model drugs. The tableting properties of the binary and ternary mixtures of the drug/starch/excpients were assessed using the 3-D modeling parameters. The crushing force (CF) of the tablets and the drug release properties were evaluated. The effect of dicalcium phosphate dihydrate on the compaction and drug release properties of the matrices was also investigated. The results obtained indicate that the tablet formation properties of the starches depend on the *Dioscorea* starch used and on the concentration of drug present in the matrix tablets. There appears to be a decrease in the CF of the tablets as the concentration of drug in the matrix is increased. Inclusion of dicalcium phosphate dihydrate in the tablet matrix increased the bonding in the matrix tablets leading to an increase in CF of the tablets. The drug release from the matrices, and the release rates and mechanism were also dependent on the *Dioscorea* starch used and the drug concentration. Modified Bitter Yam starch matrices provided a controlled release of diclofenac for up to 5 hours while modified Chinese Yam starches provided controlled release for over 24 hours. The release mechanism from modified Chinese Yam starch matrices was found to be Super Case-II transport or time-independent release kinetics. Furthermore, the release rates were dependent on the concentration of the drug present in the matrix. Thus, the modified starch matrices could be used to achieve different drug release profiles depending on the intended use of the tablets. The addition of dicalcium phosphate dihydrate not only improved the mechanical properties of the tablets but also altered the release rates and kinetics. Thus, modified Chinese Yam and Bitter Yam starches could find application as excipients for controlled drug delivery.

KEY WORDS: *Dioscorea*, yam, pregelatinized, freeze dried, starch, sustained release, diclofenac, tablets

INTRODUCTION

Starch is one of the most widely used excipients in the manufacture of solid dosage forms and can be used in formulations as filler, a disintegrant, or a binder (1). Native starches have not been used in direct compression due to compaction problems and this has limited their wide application and industrial use (2). Physical and chemical modifications have been used to improve the compaction properties of some native starches, and have yielded starches with better disintegration properties, and some

* Corresponding author: Katharina M. Picker-Freyer, Martin-Luther-University Halle-Wittenberg, Institute of Pharmacy, Div. of Pharmaceutics and Biopharmaceutics, Wolfgang-Langenbeck-Str. 4, 06120 Halle/Saale, Germany, E-mail: katharina.picker-freyer@pharmazie.uni-halle.de

have been found to be useful for sustained release dosage forms (1, 3 - 9). Typical physical modifications include pregelatinization, particle size and moisture adjustment (3 - 5). Physical modification of fully or partially gelatinized starch followed by freeze drying has produced starches useful as matrix forming materials for the formulation of sustained release tablets (1, 4). This is largely due to the cold water-swelling capacity and gel barrier formation properties of the starches (10). Pregelatinized starches retain their capillary activity and swell to some degree when in contact with water which is in contrast to other modified starches (11).

Previous studies have investigated the material and tablet formation properties of pregelatinized (thermally modified) forms of four tropical *Dioscorea* (yam) species, White yam (*Dioscorea rotundata*), Bitter yam (*D. dumetorum*), Chinese yam (*D. oppositifolia*) and Water yam (*D. alata*) (12). The *Dioscorea* starches which were fully pregelatinized followed by either oven drying (PS) or freeze drying (FD) were used as excipients in direct compression. The results showed that pregelatinization improved the compressibility and flowability of the native starches. The freeze dried pregelatinized starches generally showed higher compactibility compared to the oven dried forms. Furthermore, the pregelatinized freeze dried forms of Chinese and Bitter yam starches produced tablets which were non disintegrating indicating a potential for application as excipients for controlled drug delivery.

Most studies on the production of modified starches for sustained release matrices have been limited to widely available starches such as corn, potato, wheat, tapioca and rice (4 - 6, 8). To date, no work has been done to evaluate the usefulness of thermally modified *Dioscorea* starches as directly compressible matrix systems for sustained release applications. Thus in the present study, the freeze dried pregelatinized forms of Chinese and Bitter yam starches were evaluated as directly compressible matrix systems for application in sustained release using diclofenac and caffeine as the model drugs with different solubilities. The effects of the drug on the tablet formation properties were assessed using the 3-D modeling parameters while the tablet properties were evaluated using elastic recovery, crushing force and dissolution. An attempt was made to determine the release mechanism(s) and to evaluate the effects of a widely used tablet excipient, dicalcium phosphate dihydrate, on the release properties from the modified starch matrix tablets.

MATERIALS

The materials used were: diclofenac sodium Lot No. 22679462 (Caesar and Loretz GmbH, Hilden, Germany), caffeine Lot No. 28620028 (Carl Roth GmbH, Karlsruhe, Germany), dicalcium phosphate dihydrate Lot No. 8082 (Penwest Co, Patterson, NY, USA) and starch produced from the tubers of two different *Dioscorea* species namely Bitter yam - *D. dumetorum* Kunth and Chinese yam – *D. oppositifolia* L. which were obtained from local farmers in Ibadan, Nigeria. A description of the extraction and modification processes for the starches has been given elsewhere (12). All materials and tablets were equilibrated, produced and stored at 22 ± 1 °C and 45 ± 2 % relative humidity (RH).

METHODS

Preparation of Mixtures

100g batches of the formulation of the starches and diclofenac with or without dicalcium phosphate dihydrate were dry-mixed for 10 minutes in a cube mixer (Erweka AR 400, Erweka GmbH, Heusenstamm, Germany). The degree of mixing of the powders was determined by chemical assay for diclofenac (BP 1998) and was found to be > 0.96. For the determination degree of mixing, multiple samples were taken randomly from the same batch, and assayed for uniformity of content. Five samples was taken in each case.

Apparent particle densities were determined using a helium pycnometer (Micrometer AccuPyc 1330, Micromeritic Instruments Inc. Corp. Norcross, USA).

AccuPyc 1330, Micromeritic Instruments Inc. Corp. Norcross, USA).
The mixtures were prepared to assess the following: effect of drug concentration - mixtures prepared containing 5, 10, 20, and 40 % w/w diclofenac; effect of excipients - mixtures containing dicalcium phosphate dihydrate in the ratio of drug:starch:excipient of 1:3:1; effect of drug solubility - mixtures containing caffeine in the drug: polymer ratio of 1:4.

Tableting

Tablets were prepared using an instrumented eccentric tableting machine (EK0/DMS, No. 1.0083.92; Korsch GmbH, Germany fitted with an inductive transducer W20 TK; Spectris GmbH, Germany) fitted with 11 mm diameter flat faced punches (Ritter GmbH, Germany). The machine was instrumented for pressure and displacement measurement. Displacement measurement was corrected for elastic punch and machine deformation. Equal volumes of the substances, based on apparent particle density, were tableted to different graded maximum relative densities ($\rho_{rel,\ max}$) of the tablets (precision 0.001) between 0.75 and 0.95. No lubricant was used. The amount of material necessary for each tablet with a given $\rho_{rel,\ max}$ was calculated. The powder was manually filled into the die and one compaction cycle was performed. The minimum tablet height under load was held constant at 3 mm and the depth of filling at 13 mm. The production rate was set to 10 tablets per min.

Ten single tablets were made at each condition and force, time and displacement of the upper punch were recorded for each compaction cycle. Data were acquired using a DMC-plus system (Hottinger Baldwin Messtechnik) and were stored using BEAM-Software (AMS, Flöha, Germany). Tableting was performed in a climate-controlled room, which was set to 22 ± 1 °C and 45 % ± 2 % RH.

Compaction data analysis

3-D model

Using the 3-D modeling technique normalized time, pressure and $ln(1/1\text{-}D_{rel})$ according to Heckel were presented in a 3-D data plot, to which, a twisted plane was fitted by the least-squares method according to Levenberg-Marquardt (Matlab, The MathWorks Inc, Unterföhrung, Germany) (13).

$$z = \ln\left(\frac{1}{1-D_{rel}}\right) = (t - t_{max}) \cdot (d + \omega \cdot (p_{max} - p)) + (e \cdot p) + (f + d \cdot t_{max}) \quad \text{Eq. 1}$$

where D_{rel} = relative density, t = time and p = pressure

$$d = \frac{\delta \ln(1/1 - D_{rel}))}{\delta t}, e = \frac{\delta(1/1 - D_{rel}))}{\delta p}, f = \ln\ (\frac{1}{1 - D_{rel}})$$

t_{max} = time at maximum pressure, p_{max} = the maximum pressure and ω = twisting angle at t_{max}.

The plane is twisted at $t=t_{max}$. Time plasticity (d), pressure plasticity (e), and fast elastic decompression, the inverse of ω, of the compaction cycles at each tableting condition (material and a given $\rho_{rel,\ max}$) were obtained and the means and standard deviations were calculated.

Tablet Properties

Elastic recovery after tableting was calculated using the equation of Armstrong *et al.* (14):

$$ER\ (\%) = 100\ \frac{H_1 - H_0}{H_0} \quad \text{Eq. 2}$$

where ER = elastic recovery, H_1 = height of the tablet after 10 days, and H_0 = minimal height of the tablet under load.

Ten tablets were analyzed, and the means and standard deviations were calculated.

Crushing force

The crushing force of the tablets was determined with the crushing force tester (TBH 30; Erweka GmbH, Germany). Five tablets were analysed up to 10 days after tableting, and the means and standard deviations were calculated.

Dissolution testing

For tablets produced at $\rho_{rel,\ max}$ of 0.85 dissolution was carried out using the USP XXIII basket method (PTW II, Pharmatest, Hainburg, Germany) at 100rpm. The dissolution test was conducted in 750 mL of 0.1N hydrochloric acid (pH 1.2) at 37 °C for 2 h (acid phase) followed by the addition of 250 mL of 0.2 M sodium phosphate buffer and any further pH adjustment required to neutralize the pH to approximately 6.8 ± 0.05 (buffer phase). 5 ml samples were withdrawn and replaced with fresh medium at fixed time intervals. The sample was diluted and the amount of diclofenac or caffeine released was determined using a UV spectrophotometer (Spectronic 601, Milton Roy, PA, USA) at the wavelengths of 276 and 275 nm respectively.

Dissolution data Analysis

The dissolution data were fitted according to the equation of Korsmeyer *et al.* (15) which is often used to describe the drug release behaviour from polymeric systems:

$$\frac{M_t}{M_\infty} = Kt^n \qquad \text{Eq. 3}$$

where M_t/M_∞ is the fraction of drug released at time t, k is the kinetic constant (with unit t^{-n}) incorporating the properties of the polymeric system and the drug and *n* is the release exponent, which indicates the mechanism of release. This equation can be used to analyse the first 60% of a release curve where the release is linearly related to t^n, regardless of the geometric shape. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical exponential gradient while the Case-II relaxational release is the drug transport mechanism associated with stresses and state–transition in hydrophilic glassy polymers, which swell in water or biological fluids. This term also includes polymer disentanglement and erosion (16, 17).

Statistical analysis

The data were analyzed using analysis of variance (ANOVA) by means of GraphPad Prism® 4 software (GraphPad Software Inc. San Diego, USA). Tukey-Kramers multiple comparison tests was used to compare the material and tablet properties of the various starches. Values of p less than or equal to 0.05 were considered significant.

RESULTS AND DISCUSSION

Tableting properties

The tableting behaviour of the modified starch matrices containing different concentration of diclofenac sodium and caffeine was characterized by 3-D modeling which allows the simultaneous evaluation of the three most important tableting process variables (normalized time, pressure and density) (18). The 3-D parameter plots of the starches are given in Figure 1, while the parameters and their standard deviations are shown in Table 1.

For all mixtures of modified starches, the time plasticity (d) increased with increasing $\rho_{rel,\ max}$ up to $\rho_{rel,\ max}$ of 0.9 or 0.95. Pressure plasticity (e) decreases at all drug concentrations and the angle of torsion (ω) exhibits a minimum at $\rho_{rel,\ max}$ of 0.9 for all drug concentrations. Time plasticity (d) also tended to increase with drug concentration and it was greater for Chinese than for Bitter Yam starch. Increasing time plasticity indicates faster deformation during tableting while decreasing pressure plasticity indicates less pressure-dependent deformation. Furthermore, the starch matrix mixtures exhibited a strong increase in ω between $\rho_{rel,\ max}$ of

Table 1 The 3-D modelling parameters for mixtures of modified Dioscorea Yam starches containing different drug concentration and excipient (Mean ±SD, n = 5)

Drug conc. (%w/w)	$\rho_{rel.max}$	d	e	ω	Drug conc. (%w/w)	$\rho_{rel.max}$	d	e	ω
MODIFIED BITTER YAM STARCH					MODIFIED CHINESE YAM STARCH				
0	0.75	0.9676(0.0062)	0.0044(0.0001)	0.0166(0.0002)	0	0.75	1.0627(0.0083)	0.0052(0.0001)	0.0172(0.0004)
	0.80	1.2332(0.0160)	0.0041(0.0001)	0.0144(0.0003)		0.80	1.3728(0.0159)	0.0048(0.0001)	0.0135(0.0001)
	0.85	1.5843(0.0214)	0.0038(0.0001)	0.0129(0.0002)		0.85	1.7592(0.0120)	0.0045(0.0000)	0.0121(0.0001)
	0.90	1.9986(0.0163)	0.0035(0.0001)	0.0129(0.0003)		0.90	2.3681(0.0668)	0.0044(0.0002)	0.0107(0.0012)
	0.95	1.3134(0.0326)	0.0023(0.0000)	0.0165(0.0003)		0.95	3.2421 (0.1040)	0.0039(0.0001)	0.0153(0.0009)
5	0.75	0.6613(0.0078)	0.0053(0.0002)	0.0124(0.0003)	5	0.75	0.9540(0.0141)	0.0055(0.0000)	0.0136(0.0001)
	0.80	0.8787(0.0068)	0.0047(0.0001)	0.0115(0.0001)		0.80	1.2714(0.0125)	0.0052(0.0001)	0.0123(0.0001)
	0.85	1.1690(0.0051)	0.0043(0.0000)	0.0111(0.0002)		0.85	1.7049(0.0220)	0.0050(0.0000)	0.0110(0.0002)
	0.90	1.5816(0.0386)	0.0038(0.0000)	0.0111(0.0007)		0.90	2.2990(0.0298)	0.0048(0.0000)	0.0110(0.0002)
	0.95	1.5558(0.0454)	0.0027(0.0000)	0.0152(0.0004)		0.95	2.6527(0.0223)	0.0043(0.0000)	0.0150(0.0002)
10	0.75	0.6668(0.0081)	0.0051(0.0000)	0.0131(0.0002)	10	0.75	0.9597(0.0078)	0.0058(0.0000)	0.0137(0.0002)
	0.80	0.8916(0.0123)	0.0047(0.0000)	0.0119(0.0002)		0.80	1.2730(0.0122)	0.0055(0.0001)	0.0122(0.0001)
	0.85	1.2113(0.0150)	0.0044(0.0000)	0.0107(0.0002)		0.85	1.6981(0.0058)	0.0053(0.0000)	0.0108(0.0002)
	0.90	1.5980(0.0212)	0.0040(0.0001)	0.0104(0.0002)		0.90	2.2908(0.0426)	0.0050(0.0001)	0.0108(0.0007)
	0.95	1.5959(0.0629)	0.0030(0.0002)	0.0146(0.0004)		0.95	3.0163 (0.0265)	0.0048(0.0000)	0.0120(0.0005)
20	0.75	0.6327(0.0056)	0.0053(0.0001)	0.0141(0.0001)	20	0.75	0.8197(0.0058)	0.0058(0.0000)	0.0134(0.0001)
	0.80	0.8478(0.0069)	0.0048(0.0001)	0.0128(0.0002)		0.80	1.0845(0.0060)	0.0054(0.0000)	0.0121(0.0001)
	0.85	1.1171(0.0079)	0.0044(0.0002)	0.0119(0.0003)		0.85	1.4616(0.0071)	0.0051(0.0000)	0.0108(0.0001)
	0.90	1.5307(0.0284)	0.0040(0.0000)	0.0111(0.0003)		0.90	2.0905(0.0134)	0.0049(0.0001)	0.0090(0.0003)
	0.95	1.9552(0.0405)	0.0035(0.0001)	0.0120(0.0003)		0.95	2.8344(0.0427)	0.0046(0.0000)	0.0113(0.0003)
40	0.75	0.5546(0.0037)	0.0051(0.0000)	0.0153(0.0002)	40	0.75	0.6528(0.0035)	0.0054(0.0000)	0.0130(0.0002)
	0.80	0.7488(0.0120)	0.0046(0.0000)	0.0130(0.0003)		0.80	0.8938(0.0065)	0.0051(0.0000)	0.0113(0.0001)
	0.85	1.0590(0.0042)	0.0043(0.0000)	0.0106(0.0001)		0.85	1.2434(0.0096)	0.0048(0.0001)	0.0098(0.0002)
	0.90	1.5015(0.0272)	0.0040(0.0001)	0.0098(0.0004)		0.90	1.7346(0.0111)	0.0046(0.0000)	0.0089(0.0003)
	0.95	2.1119(0.0233)	0.0037(0.0001)	0.0097(0.0004)		0.95	2.5216(0.0146)	0.0040(0.0002)	0.0101(0.0018)
[a]20	0.75	0.6389(0.0026)	0.0045(0.0002)	0.0143(0.0007)	[a]20	0.75	0. 7240(0.0036)	0.0049(0.0001)	0.0147(0.0002)
	0.80	0.8751(0.0016)	0.0041(0.0001)	0.0124(0.0003)		0.80	0.9518(0.0113)	0.0046(0.0000)	0.0136(0.0001)
	0.85	1.1860(0.0162)	0.0039(0.0000)	0.0105(0.0001)		0.85	1.3080(0.0163)	0.0043(0.0000)	0.0127(0.0002)
	0.90	1.6198(0.0229)	0.0037(0.0000)	0.0095(0.0002)		0.90	1.7835(0.0143)	0.0041(0.0000)	0.0119(0.0001)
	0.95	1.8256(0.0841)	0.0031(0.0000)	0.0112(0.0006)		0.95	2.4557(0.0510)	0.0039(0.0001)	0.0123(0.0002)
[b]20	0.75	0.9676(0.0062)	0.0044(0.0001)	0.0166(0.0002)	[b]20	0.75	1.0627(0.0083)	0.0052(0.0001)	0.0172(0.0004)
	0.80	1.2332(0.0160)	0.0041(0.0001)	0.0144(0.0003)		0.80	1.3728(0.0159)	0.0048(0.0001)	0.0135(0.0001)
	0.85	1.5843(0.0214)	0.0038(0.0001)	0.0129(0.0002)		0.85	1.7592(0.0120)	0.0045(0.0000)	0.0121(0.0001)
	0.90	1.9986(0.0163)	0.0035(0.0001)	0.0129(0.0003)		0.90	2.3681(0.0668)	0.0044(0.0002)	0.0107(0.0012)
	0.95	1.3134(0.0326)	0.0023(0.0000)	0.0165(0.0003)		0.95	3.2421(0.1040)	0.0039(0.0001)	0.0153(0.0009)

[a]Caffeine; [b] addition of 20 % dicalcium phosphate dihydrate with diclofenac

0.90 and 0.95 while the d-value increased for modified Chinese Yam starch and decreased for modified Bitter Yam starch matrix mixtures. This indicates a change in deformation properties of these starches, possibly due to a change in material properties similar to previous results (12, 19). However, the d-value increased between $\rho_{rel,\ max}$ of 0.90 and 0.95 for modified Bitter Yam starch matrix mixtures containing 20-40% diclofenac. This indicates that the time dependent deformation of the modified starch matrices is affected by the concentration of drug present in the tablet and depends at these concentrations also on the deformation properties of the drug. The pressure plasticity (e) was higher for modified Chinese Yam starch matrix mixtures. This indicates that modified Chinese Yam starch deforms more easily without a lot of pressure than the modified Bitter Yam starch matrix mixtures. The fast elastic deformation 1/ω, increased with increase in drug concentration,

which indicates that the drug affected the elasticity of the starches during tableting due to its own elasticity. Pregelatinized starch has been reported to have good compression properties and deforms mainly plastically as described for fully pregelatinized starch (20, 21).

The shape of the 3-D plots indicates that the modified Bitter Yam Starch matrix mixtures generally show flat plots with a slight decrease in ω values, and the slope of the plot depended on the concentration of drug present in the matrices (Figure 1A). This suggests a more homogenous bonding facilitating deformation and is similar to the behaviour of other materials such as microcrystalline cellulose (18). The modified Chinese Yam starch matrix mixtures (Figure 1B) showed a strong decrease in ω values with increase in drug concentration suggesting brittle fracture of the material which enhances the formation of new surfaces and thus enhances the formation of bonds between particles (22). For the modified Chinese Yam starch matrix mixtures, the strong increase in ω between $\rho_{rel, max}$ of 0.90 and 0.95 while the d value which appeared as a 'kink' in the 3-D plot gradually decreased with increase in drug concentration.

There was also a slight change in the 3-D parameters when the model drug was changed to caffeine which is due to the more plastic deformation character of the drug (Figure 2). When a directly compressible predominantly brittle excipient, dicalcium phoshate dihydrate was added into the tablet formulation (Figure 2), the 3-D parameters changed to lower d-, e- and ω-values and a steeper plot.

The steepness of the plots indicates that dicalcium phosphate dihydrate which deforms by brittle fracture contributes significantly to the deformation properties of the starch mixes. The plot becomes steeper with strongly decreasing ω value and thi s is indicative of less homogenous deformation compared to the matrices containing no dicalsium phosphate dihydrate.

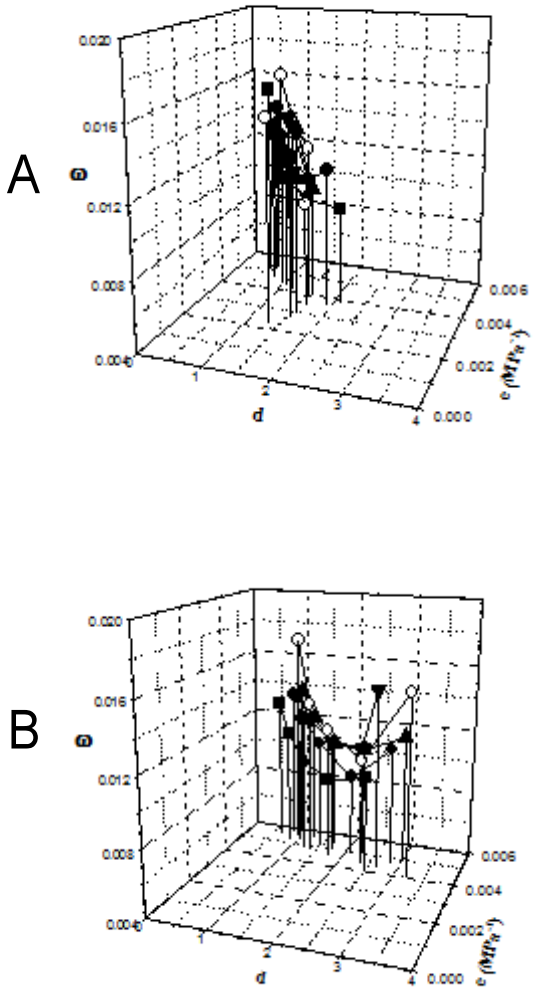

Figure 1 3-D parameter plot for modified Bitter Yam starch (A) and modified Chinese Yam starch (B) matrices containing different concentration of diclofenac: ▽- 0%; ○ - 5%; ▲ - 10%; ● - 20%; ■ - 40%.

Tablet properties

The elastic recovery of the tablets was determined at various times and the results are shown in Table 2.The fast elastic recovery (FER) increased with time but decreased with increasing $\rho_{rel, max}$ The elastic recovery of the starch tablets increased with storage with modified Bitter Yam starch tablet formulations showing higher ER than those containing modified Chinese Yam starch after 10 days.

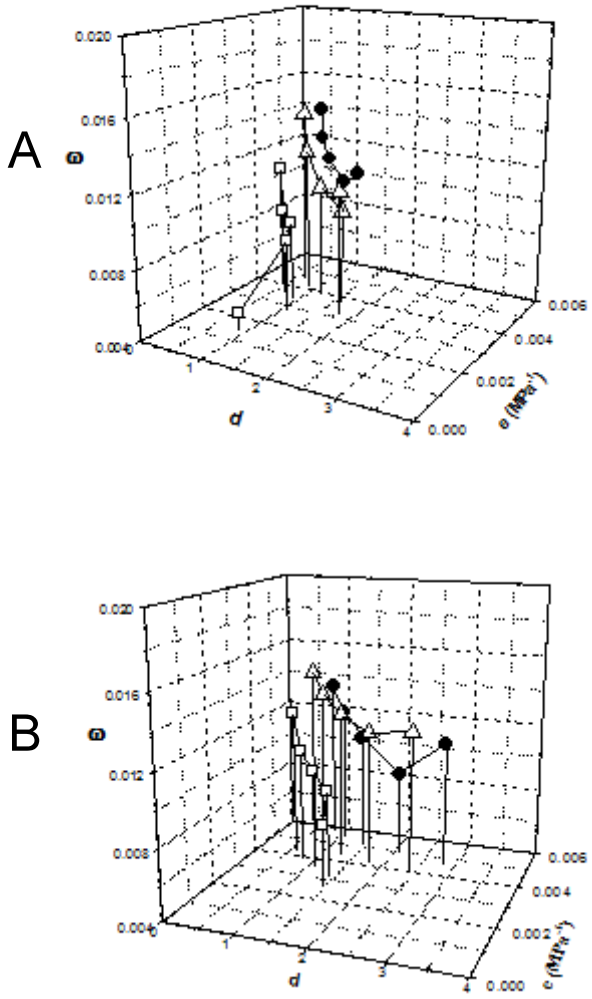

Figure 2 3-D parameter plot for modified Bitter Yam starch (A) and modified Chinese Yam starch (B) matrices containing ● - 20% diclofenac, ▽- 20% Caffeine, □ - 20% diclofenac and 20% dicalcium phosphate dihydrate ($\rho_{rel, max}$ of 0.85)

The ER generally increased with drug concentration but showed a decrease at drug concentration of 40%. However, when the dicalcium phosphate dihydrate was added to the tablet matrix, and when model drug was changed to caffeine, there was a sharp decrease in ER. This indicated that matrices containing caffeine and dicalcium phosphate dihydrate show less elastic recovery on storage than those containing diclofenac.

The CF of the tablets are presented in Table 3 The CF of the tablets generally increased with increase in $\rho_{rel, max}$ and compression pressure. The modified starches which exhibited crushing strength values higher than 500N at $\rho_{rel, max}$ of 0.85 and above, gradually showed a decrease in the CF values as the concentration of the drug increases in the matrix tablets. This indicates a weakening in bonding between the particles. Previous studies have shown that there was complete deformation of the particles, and formation of a gel like network of the modified starches (12). The high specific surface area of the starches facilitated more contact between the particles, the formation of stronger bonds and the formation of a completely new network-like structure. The particles are very deformed and appear to be 'fused' together (12). However, as the drug is added, there is 'contamination' of these surfaces which prevents the formation of the network-like structure and thus there is a decrease in the CF of the tablets. The CF was also significantly ($p<0.05$) greater when caffeine was used as the model drug than when diclofenac was used at the same concentration. This was expected since caffeine matrices showed less elastic recovery and more plasticity.

The addition of directly compressible excipients has been used not only to alter the tablet size but also to improve the compaction and mechanical properties of the tablet (17). Thus, dicalcium phosphate dihydrate was used in the ratio of drug:starch:excipient of 1:3:1. There was a general decrease in CF of the matrix tablets when the excipient was added compared to the matrices containing 20% of the drug indicating the disturbance of the homogeneous tablet Yam starch matrix structure in which the drug was embedded. However, the CF was significantly higher for tablets containing excipient when compared with matrices containing 40% diclofenac since diclofenac is not a directly compressible drug which is able

Table 2 Elastic Recovery (ER) at different $\rho_{rel,max}$ for mixtures of modified *Dioscorea* Yam starches containing different drug concentration and excipient (Mean ±SD, n = 10)

Drug conc. (%w/w) MODIFIED BITTER YAM STARCH	$P_{rel.max}$	Fast ER (%)	ER after ejection (%)	ER after 1hr (%)	ER after 10days (%)	Drug conc. (%w/w) MODIFIED CHINESE YAM STARCH	$P_{rel.max}$	Fast ER (%)	ER after ejection (%)	ER after 1hr (%)	ER after 10days (%)
0	0.75	2.43(0.03)	11.32(0.54)	12.60(0.31)	13.23(0.16)	0	0.75	2.36(0.05)	12.15(0.24)	13.78(0.17)	14.54(0.11)
	0.80	2.46(0.03)	10.50(0.23)	11.55(0.36)	12.14(0.18)		0.80	2.40(0.02)	11.85(0.24)	13.28(0.28)	13.77(0.24)
	0.85	2.47(0.02)	10.25(0.10)	10.75(0.35)	11.53(0.74)		0.85	2.40(0.01)	11.11(0.24)	12.27(0.19)	12.86(0.27)
	0.90	2.54(0.05)	9.27(0.38)	10.12(0.41)	10.59(0.37)		0.90	2.43(0.02)	10.46(0.37)	11.37(0.28)	12.01(0.33)
	0.95	2.31(0.04)	8.85(0.18)	9.49(0.22)	10.07(0.58)		0.95	2.28(0.01)	9.86(0.24)	10.47(0.26)	11.15(0.26)
5	0.75	2.39(0.02)	14.14(0.32)	17.03(0.13)	18.72(0.14)	5	0.75	2.36(0.05)	11.41(0.24)	13.50(0.17)	15.14(0.11)
	0.80	2.52(0.01)	13.05 (0.21)	15.64(0.19)	17.47(0.12)		0.80	2.48(0.02)	11.35(0.24)	13.12(0.28)	14.55(0.24)
	0.85	2.64(0.05)	12.26(0.18)	14.46(0.19)	15.92(0.17)		0.85	2.53(0.01)	10.71(0.24)	12.30(0.19)	13.86(0.27)
	0.90	2.95(0.01)	11.66(0.12)	13.26(0.68)	14.66(0.17)		0.90	2.63(0.02)	10.60(0.37)	11.91(0.28)	13.10(0.33)
	0.95	3.23(0.03)	11.63(0.14)	12.89(0.21)	14.20(0.11)		0.95	2.98(0.01)	10.01(0.24)	11.90(0.26)	13.15(0.26)
10	0.75	2.39(0.03)	14.13(0.17)	17.84(0.21)	19.89(0.31)	10	0.75	2.72(0.03)	12.88(0.08)	15.62(0.11)	17.92(0.13)
	0.80	2.52(0.04)	13.15(0.20)	16.17(0.22)	18.41(0.21)		0.80	2.81(0.03)	12.31(0.04)	14.78(0.08)	16.94(0.09)
	0.85	2.64(0.01)	12.69(0.08)	15.17(0.09)	17.15(0.51)		0.85	2.89(0.02)	12.07(0.20)	14.10(0.11)	16.08(0.10)
	0.90	2.95(0.02)	12.12(0.16)	14.05(0.22)	15.76(0.16)		0.90	3.04(0.05)	11.79(0.21)	13.43(0.17)	15.16(0.10)
	0.95	3.23(0.01)	12.06(0.18)	13.41(0.17)	15.25(0.23)		0.95	3.48(0.04)	12.29(0.18)	13.55(0.09)	14.22(0.14)
20	0.75	2.29(0.02)	14.49(0.15)	18.14(0.13)	20.13(0.17)	20	0.75	2.65(0.03)	13.26(0.13)	16.22(0.18)	18.42(0.19)
	0.80	2.24(0.02)	13.35(0.17)	16.31(0.22)	18.17(0.26)		0.80	2.79(0.01)	12.61(0.20)	15.07(0.17)	17.24(0.20)
	0.85	2.53(0.02)	12.48(0.11)	14.87(0.09)	16.92(0.31)		0.85	2.87(0.02)	11.93(0.11)	14.12(0.08)	15.94(0.05)
	0.90	2.75(0.03)	11.89(0.08)	13.72(0.07)	15.06(0.85)		0.90	3.02(0.03)	11.07(0.20)	13.19(0.28)	15.15(0.17)
	0.95	3.11(0.01)	11.88(0.12)	13.13(0.13)	14.66(0.11)		0.95	3.45(0.03)	11.83(0.12)	13.11(0.08)	14.57(0.17)
40	0.75	1.80(0.01)	12.78(0.28)	15.57(0.28)	18.14(0.04)	40	0.75	1.74(0.10)	10.48(0.12)	12.70(0.11)	14.91(0.06)
	0.80	1.92(0.03)	11.49(0.16)	13.80(0.12)	16.13(0.05)		0.80	1.87(0.02)	9.93(0.13)	11.78(0.14)	13.98(0.18)
	0.85	2.06(0.02)	10.62(0.18)	12.27(0.15)	14.75(0.35)		0.85	2.07(0.04)	9.64(0.17)	11.17(0.16)	12.91(0.22)
	0.90	2.27(0.02)	10.00(0.11)	11.17(0.06)	13.07(0.18)		0.90	2.23(0.02)	9.38(0.22)	10.64(0.14)	12.08(0.18)
	0.95	2.73(0.01)	10.00(0.17)	10.82(0.16)	12.46(0.18)		0.95	2.11(0.03)	9.16(0.13)	10.09(0.92)	11.58(0.21)
[a]20	0.75	2.12(0.02)	10.23(0.33)	12.25(0.13))	14.23(0.20)	[a]20	0.75	2.15(0.03)	10.41(0.85)	12.59(0.33)	14.97(0.25)
	0.80	2.17(0.02)	9.65(0.33)	11.35(0.39)	13.35(0.28)		0.80	2.18(0.01)	10.20(0.15)	11.79(0.17)	13.98(0.13)
	0.85	2.12(0.02)	9.32(0.15)	10.85(0.20)	12.85(0.26)		0.85	2.23(0.02)	9.67(0.16)	10.95(0.10)	13.05(0.33)
	0.90	2.13(0.03)	9.62(1.41)	10.07(0.21)	12.11(0.38)		0.90	2.24(0.03)	9.25(0.11)	10.26(0.04)	12.37(0.46)
	0.95	3.43(0.01)	9.25(1.20)	9.64(0.23)	10.90(0.26)		0.95	2.36(0.03)	9.23(1.02)	10.07(0.50)	11.38(0.23)
[b]20	0.75	2.43(0.03)	11.32(0.54)	12.60(0.31)	13.23(0.16)	[b]20	0.75	2.36(0.05)	12.15(0.24)	13.78(0.17)	14.54(0.11)
	0.80	2.46(0.03)	10.50(0.23)	11.55(0.36)	12.14(0.18)		0.80	2.40(0.02)	11.85(0.24)	13.28(0.28)	13.77(0.24)
	0.85	2.47(0.02)	10.25(0.10)	10.75(0.35)	11.53(0.74)		0.85	2.40(0.01)	11.11(0.24)	12.27(0.19)	12.86(0.27)
	0.90	2.54(0.05)	9.27(0.38)	10.12(0.41)	10.59(0.37)		0.90	2.43(0.02)	10.46(0.37)	11.37(0.28)	12.01(0.33)
	0.95	2.31(0.04)	8.85(0.18)	9.49(0.22)	10.07(0.58)		0.95	2.28(0.01)	9.86(0.24)	10.47(0.26)	11.15(0.26)

[a] Caffeine; [b] addition of 20 % dicalcium phosphate dihydrate with diclofenac

to from an own tablet matrix. In conclusion dicalcium phosphate dihydrate improves bond formation.

Drug release properties

Release profiles from the modified starch matrix tablets containing 20% diclofenac sodium are presented in Figure 3 and the amount of drug released at various time intervals is presented in Table 4.

There was a lag time at the start of the dissolution test probably due to the insolubility of diclofenac sodium at acidic pH. However the increase in solubility of the drug at basic pH led to erosion/diffusion of the drug from the matrix (23). There was a significant difference in the drug release properties from the matrix tablets prepared with the two modified starches with modified Chinese Yam starch matrices showing significantly ($p<0.05$) slower release rates. Although modified Bitter Yam starch when compressed on its own formed tablets which were non-disintegrating, when the drug was added, the tablets became subject to erosion/diffusion/disintegration. The drug release from the modified Bitter Yam starch matrix tablets occurred over 5 hours and the amount released depended on the concentration of drug present in the matrix system. Modified Chinese Yam starch on the other hand provided a non disintegrating matrix system. The release profiles for the modified Chinese Yam starch matrix tablets

Table 3 Crushing strength of modified *Dioscorea* Yam starch matrices containing different concentration diclofenac (Mean ±SD, n = 5)

Drug concentration (%w/w)	$\rho_{rel.max}$	CS (N)	Drug concentration (%w/w)	$\rho_{rel.max}$	CS (N)
MODIFIED BITTER YAM STARCH			MODIFIED CHINESE YAM STARCH		
0	0.85	283.0(17.3)	0	0.75	320.8(32.0)
	0.95	386.0(34.0)		0.80	404.8(20.3)
	0.85	-		0.85	-
	0.90	-		0.90	-
	0.95	-		0.95	-
5	0.75	115.4(4.4)	5	0.75	273.2(19.8)
	0.80	182.2(7.8)		0.80	330.4(18.2)
	0.85	270.2(5.3)		0.85	445.8(20.0)
	0.90	369.4(10.9)		0.90	-
	0.95	-		0.95	-
10	0.75	86.2(5.1)	10	0.75	193.6(9.5)
	0.80	136.8(5.9)		0.80	278.6(4.3)
	0.85	202.0(5.5)		0.85	346.6(6.6)
	0.90	303.0(3.1)		0.90	444.8(13.8)
	0.95	414.2(10.5)		0.95	-
20	0.75	63.8(4.4)	20	0.75	126.8(5.9)
	0.80	106.8(5.9)		0.80	177.8(7.3)
	0.85	163.2(5.2)		0.85	242.4(6.7)
	0.90	241.0(3.3)		0.90	330.4(13.0)
	0.95	346.6(6.6)		0.95	428.6(17.7)
40	0.75	38.2 (1.8)	40	0.75	84.8(4.1)
	0.80	70.6 (3.1)		0.80	122.2(6.5)
	0.85	132.0 (1.8)		0.85	170.0(5.8)
	0.90	184.2(2.2)		0.90	238.2(6.7)
	0.95	280.0(8.8)		0.95	335.2(7.0)
[a]20	0.75	118.8(13.2)	[a]20	0.75	184.8(5.6)
	0.80	191.2(8.3)		0.80	245.4(7.0)
	0.85	266.4(7.1)		0.85	329.0(18.5)
	0.90	384.2(11.9)		0.90	444.8(19.5)
	0.95	-		0.95	-
[b]20	0.75	48.2(4.1)	[b]20	0.75	98.0 (2.1)
	0.80	75.6(5.8)		0.80	147.8 (5.9)
	0.85	135.8(3.9)		0.85	200.2 (3.0)
	0.90	198.6(6.2)		0.90	285.2 (5.9)
	0.95	358.8(7.4)		0.95	407.2 (8.4)

- Crushing strength value > 500N
[a] Caffeine; [b] addition of 20 % dicalcium phosphate dihydrate with diclofenac

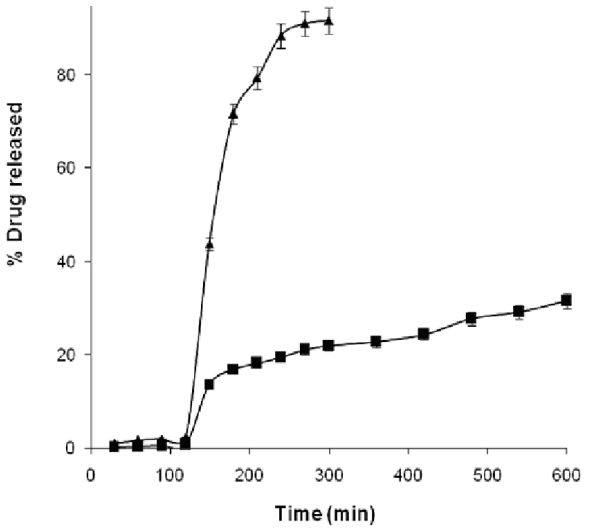

Figure 3 Release profile of diclofenac sodium from modified Yam starch matrices containing 20% drug concentration ($\rho_{rel, max}$ of 0.85, mean ± SD; n = 3) ▲ - modified Bitter Yam starch; ■ - Modified Chinese Yam starch

containing different concentration of diclofenac are presented in Figure 4.

The highest concentration of drug released was 85% after 10 hours for matrices containing 40% diclofenac. At lower drug concentrations, less than 50% of the drug was released after 24 hours. Thus, modified Chinese Yam starch matrices could be useful in providing sustained drug release for over 24 hours. The increased

Table 4 Amount of drug released (%) at various time intervals for modified *Dioscorea* starch matrices (Mean ±SD, n = 5), (Mean and SD, n = 5)

Drug conc. (%w/w)	$\rho_{rel.max}$	2h	5h	10h	Drug conc. (%w/w)	$\rho_{rel.max}$	2h	5h	10h
MODIFIED BITTER YAM STARCH					MODIFIED CHINESE YAM STARCH				
5	0.85	8.14(0.25)	104.51(1.08)	-	5	0.85	2.99(0.72)	28.38(0.75)	43.15(2.31)
	0.95	5.65(0.65)	104.17(2.28)	-		0.95	1.89(1.50)	24.79(0.73)	33.77(1.24)
10	0.85	7.02(0.42)	100.03(1.22)	-	10	0.85	2.25(0. 38)	30.84(0.51)	43.80(1.22)
	0.95	5.23(0.52)	99.21(1.56)	-		0.95	1.13(0.72)	24.17(0.38)	40.07(0.90)
20	0.85	2.80(0.28)	94.25(0.06)	-	20	0.85	1.99(0.72)	26.62(1.05)	61.15(0.32)
	0.95	2.23(0.42)	91.55(0.09)	-		0.95	1.78(0.21)	21.95(0.73)	31.51(0.48)
40	0.85	1.89 (0.14)	90.91(0.90)	-	40	0.85	4.42(0. 38)	59.52(0.51)	85.30(1.61)
	0.95	1.87 (0.05)	73.16(1.49)	-		0.95	3.43(0.72)	44.14(0.08)	75.35(1.67)
[a]20	0.95	53.48(2.57)	98.08(2.91)	-	[a]20	0.95	52.23(0.72)	78.35(0.80)	97.68(0.01)
[b]20	0.95	2.48(2.57)	101.61(1.69)	-	[b]20	0.95	1.51(2.57)	101.73(1.69)	-

[a] Caffeine, [b] addition of 20 % dicalcium phosphate dihydrate with diclofenac

dissolution rate in tablets containing 40 %w/w of diclofenac may probably be due to the weakening of the matrix lattice due to the high concentration of the drug, which provides a diffusion pathway for diffusion/erosion/ disintegration of the matrix. The release parameters according to Korsmeyer *et al.* (15) (Eq. 3) are presented in Table 5.

The high values of the coefficient of linear regression confirm that the data treatment may be used to predict the release rates from the modified starch matrices. For modified Bitter Yam starch matrices, the release mechanism for 5% drug concentration was Fickian diffusion but became anomalous (non-Fickian) as the concentration of the drug is increased to 10%. When the concentration was increased to 20%, the release mechanism became Case II transport. Thus modified Bitter Yam starch matrices containing 20 and 40% diclofenac showed Super Case-II transport or time-independent release kinetics with n = 0.982 and 1.826 respectively. Modified Bitter Yam starch, when in contact with the dissolution medium, hydrates and forms a gel which is gradually eroded although the particles were insoluble in the dissolution medium. On the other hand, modified Chinese Yam starch matrices containing 5-20% of diclofenac showed anomalous (non-Fickian) but approaches Case-II transport or time-independent release kinetics as the concentration of drug is decreased. Modified Chinese Yam starch matrices containing 40% drug showed a Fickian release mechanism with n = 0.003. The release appeared to be controlled by diffusion of the drug from the matrix into the dissolution medium. Thus, the two modified starches behaved very differently in their drug release properties which depended on the concentration of drug present in the matrix.

The release profiles from the modified starch matrix tablets containing 20% caffeine are presented in Figure 5 and the amount of drug released at various time interval are presented in Table 4.

Table 5 Release parameters derived from the Korsmeyer equation for modified *Dioscorea* starch matrices at various time intervals (Mean and SD, n = 5)

Starch	Drug conc. (%w/w)	Release exponent (n)	Kinetics constant (k) (min^{-n})	r^2
MODIFIED BITTER YAM STARCH	5	0.405(0.012)	102.32(1.01)	0.948
	10	0.597(0.004)	35.00(0.98)	0.949
	20	0.982(0.001)	3.78(0.06)	0.900
	40	1.826(0.013)	0.02(0.01)	0.972
	[a]20	0.667(0.007)	2.77(0.61)	0.985
	[b]20	0.678(0.002)	2.39(0.23)	0.944
MODIFIED CHINESE YAM STARCH	5	0.702(0.002)	4.53(0.01)	0.992
	10	0.619(0.014)	6.87(0.08)	0.993
	20	0.542(0.011)	9.68(0.12)	0.986
	40	0.003(0.010)	25.00(0.66)	0.946
	[a]20	0.394(0.17)	8.28(0.14)	0.975
	[b]20	1.875(0.002)	0.03(0.01)	0.963

[a]Caffeine, [b] addition of 20 % dicalcium phosphate dihydrate with diclofenac

The release profiles show that when a freely soluble drug, caffeine was used, there was an initial burst followed by a decrease in the release rate with increasing time which is typical of Case I diffusion behaviour, characterized by the Higuchi equation. However, the modified starches were able to provide a controlled release of caffeine for over 5 hours for modified Bitter Yam starch and 10 hours for modified Chinese Yam starch matrices (Table 4). Dissolution of caffeine from modified Chinese Yam starch matrices was by Case I or Fickian diffusion. This is similar to the mechanism of drug release reported for HPMC matrices (24). Alderman (23) described the prolonged release from HPMC as being due to the formation of a strong viscous gel when the polymer hydrates on contact with water. However, the major disadvantage of HPMC is that the drug release does not follow time-independent kinetics (24 - 26). The modified Chinese Yam starch matrix also forms a viscous gel similar to HPMC and remains insoluble in the dissolution medium but showed pores which were diffusion pathway for drug release from the matrix system.

When dicalcium phosphate dihydrate was added into the matrix tablet containing 20% diclofenac (Table 4), there was an increase in the dissolution rate of the tablets especially for

modified Chinese Yam starch matrices which released 100% of the drug in 5 hours as compared to 44% when the matrix contained 40% drug. Thus, the excipient appears to serve as a 'weakness' in the tablet matrix which serve as a diffusion pathway for the drug which means it acts as a channel and the matrix is susceptible to erosion. The excipient also altered the release mechanism of the matrix tablets. The release mechanism was zero order for modified Bitter Yam starch matrices but super case II for modified Chinese Yam starch matrices. Thus, excipients could be used not only to alter the compactibility of the modified starches, but also to alter their drug release properties.

CONCLUSION

The results obtained show the potential of modified *Dioscorea* starch matrices for sustained drug delivery. The tablet formation properties of the starches depended on the *Dioscorea* starch used and on the concentration of drug present in the matrix tablets. There appears to be a decrease in the CF of the tablets as the concentration of drug in the matrix is increased.

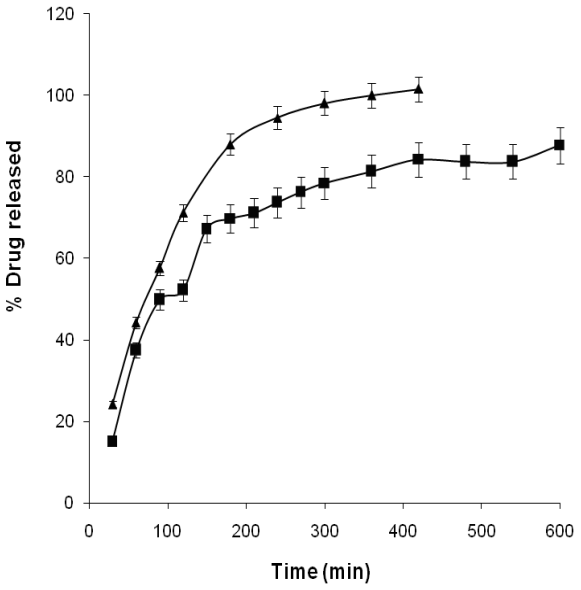

Figure 5 Release profile of caffeine from modified starch matrices containing 20% drug concentration ($\rho_{rel, max}$ of 0.85, mean ± SD; n = 3)
▲ - modified Bitter Yam starch;
■ - modified Chinese Yam starch

Inclusion of dicalcium phosphate dihydrate in the tablet matrix increased the bonding in the matrix tablets leading to an increase in CF of the tablets. The amount for drug release from the matrices, and the release rates and mechanism were also dependent on the type of *Dioscorea* starch used and the drug concentration. The modified starch matrices showed good compaction properties when compressed directly over a range of different drug concentrations. The addition of dicalcium phosphate dihydrate not only improved the mechanical properties of the tablets but also altered the release rates and kinetics. Thus, modified Chinese and Bitter Yam starches may have potential as excipients for controlled drug delivery.

ACKNOWLEDGMENTS

We gratefully acknowledge the Alexander von Humboldt Foundation for a Georg Forster Fellowship awarded to O. A. Odeku.

REFERENCES

1 Visavarungroj N, Remon JP. An evaluation of hydroxypropyl starch as disintegrant and binder in tablet formulation, Drug Dev Ind Pharm, 17 (10): 1389 – 1396, 1991.

2 BeMiller JN. Starch modification: Challenges and prospects, Starch, 49: 127- 131, 1997.

3 Nakano M, Nakazono N, Inotsume N. Preparation and evaluation of sustained release tablets prepared with alpha-starch, Chem Pharm Bull 35: 4346-4350, 1987.

4 Van Aerde P, Remon JP. In vitro evaluation of modified starches as matrices for sustained release dosgae forms, Int J Pharm, 45: 145-152, 1988.

5 Herman J, Remon JP, De Vilder J. Modified starches as hydrophilic matrices for controlled oral delivery. I. Production and characterisation of thermal modified starches, Int J Pharm, 56: 51-63, 1989.

6 Sanghvi PP, Collins CC, Shukla AJ. Evaluation of Preflo ® starches as new direct compression excipients I. Tabletting characteristics, Pharm Res, 10 (11): 1597-1603, 1993.

7 te Wierik GHP, Bergsma J, Arends-Scholte AW, Boersma T, Eissens AC, Lerk CF. A new generation of starch products as excipient in pharmaceutical tablets. I. Preparation and binding properties of high surface area potato starch products Int J Pharm 134: 27-36, 1996.

8 Van der Voort Maarschalk K, Vromans H, Groenendijk W, Bolhuis GK, Lerk CF. Effect of water on deformation and bonding of pregelatinized starch compacts, Eur J Pharm Biopharm, 44: 253-260, 1997.

9 Atichokudomchai N, Varavinit S. Characterization and utilization of acid-modified cross-linked tapioca starch in pharmaceutical tablets, Carbohyd Polymers, 53 263-270, 2003.

10 Szepes A, Makai Z, Blumer C, Mader K, Kasa P, Revesz PS. Characterization and drug delivery behaviour of starch-based hydrogels prepared via isostatic ultrahigh pressure, Carbohyd Polymers, 72 (4): 571-578, 2008.

11 Sanchez L, Torrado S, Lastres JL. Gelatinized/freeze dried starch as excipient in sustained release tablets, Int J Pharm 115: 201 – 208, 1995.

12 Odeku OA, Schmid W, Picker-Freyer KM. Material and tablet properties of pregelatinized (thermally modified) *Dioscorea* starches. European J Pharma Biopharm, 70 (1):357-371, 2008.

13 Picker KM. The 3-D Model. Comparison of Parameters Obtained From and by Simulating Different Tableting Machines, AAPS PharmSciTech. 4(3) E35, 2003.

14 Armstrong NA, Haines-Nutt RF. Elastic recovery and surface area changes in compacted powder systems, J Pharm Pharmacol, 24: 135P-136P, 1972.

15 Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers, Int J Pharm, 15: 25-35, 1983.

16 Sinclair GW, Peppas NA. Analysis of non-Fickian transport in polymers using simplified exponential expression, J Memb Sci, 17: 329-331, 1984.

17 Cox PJ, Khan KA, Munday DL, Sujja-areevath J. Development and evaluation of a multiple-unit oral sustained release dosage form for S (+)-ibuprofen: preparation and release kinetics, Int J Pharm, 193: 74-84, 1999.

18 Picker KM. The 3-D model: Explaining densification and deformation mechanisms by using 3-D parameter plots, Drug Dev Ind Pharm, 30(4): 413-425, 2004.

19 Schmid W, Picker-Freyer KM. Tableting and Tablet Behaviour of Alginates-Characterisation and Potential for Soft Tableting, Eur J Pharm Biopharm, 72(1): 165-172, 2009.

20 Olett AL, Kirby AR, Clark SA, Parker R, Smith AC. The Effect of Water Content on the Compaction Behaviour of Potato Starch, Starch, 45: 51-55, 1993.

21 Rahmouni M, Lenaerts V, Massuelle D, Doelker E., Leroux JC. Influence of physical parameters and lubricants on the compaction properties of granulated and non-granulated cross-linked high amylose starch, Chem Pharm Bull, 50 (9): 1155-1162, 2002.

22 Hauschild K, Picker-Freyer KM. Evaluation of a new coprocessed compound based on lactose and maize starch for tablet formulation, AAPS Pharm Sci, 6: Article16, 2004.

23 Alderman DA. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms, Int J Pharm Tech Prod Mfr, 5: 1-9, 1984.

24 Odeku OA, Fell JT. Evaluation of khaya gum as a directly compressible matrix system for controlled release, J Pharm Pharmacol 56 (11): 1365-1370, 2004.

25 Ford JL, Rubinstein MH, Hogan JE, Formulation of sustained release promethazine hydrochloride tablet using hydroxypropyl methylcellulose matrices, Int J Pharm, 24: 327-338, 1985.

26 Talukdar MM, Michoel A, Rombaut P, Kinget R. Comparative study on xanthan gum and hydroxypropyl methylcellulose as matrices for controlled-release drug delivery I. Compaction and in vitro drug release behaviour, Int J Pharm, 129: 233-241, 1996.