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Evaluation of Three Tropical Starches as Superdisintegrants in Fast Dissolving Tablets of Domperidone Using a Taguchi-Based Design of Experiments

ADENIKE OKUNLOLA*

Department of Pharmaceutics and Industrial Pharmacy, University of Ibadan, Ibadan, Nigeria.

A Taguchi-based design of experiments was employed to optimize fast-dissolving tablet formulations of domperidone using three starches from banana (*Musa acuminata*), cassava (*Manihot esculenta*) and Chinese yam (*Dioscorea rotundata*). The starches were modified by carboxymethylation (degree of substitution 0.32±0.02) and used as superdisintegrants (2–8%w/w), in comparison to sodium starch glycolate (SSG). Effects of two variables (superdisintegrant type and superdisintegrant concentration) at four levels on crushing strength-friability ratio (CSFR), disintegration time (DT) and dissolution time to 80% drug release (t_{80}) were analyzed. Domperidone tablets containing carboxymethylated starches had higher CSFR values ($p<0.05$) than SSG while DT and t_{80} decreased with concentration. Taguchi's delta values and analysis of variance showed that superdisintegrant type had greater influence on CSFR and t_{80} while superdisintegrant concentration had greater influence on DT. Optimum fast-dissolving domperidone tablets were obtained using 2% w/w Chinese yam starch (CSFR= 251.25±16.32) and 8% w/w SSG (DT = 0.42±0.03 min; t_{80} = 0.50±0.02 min).

KEY WORDS: Banana, cassava, Chinese yam starches, carboxymethylation, superdisintegrant, domperidone, Taguchi design

INTRODUCTION

In spite of their wide acceptability as a dosage form, a lot of people still have difficulty in swallowing conventional tablets [1,2]. This is common in paediatric, geriatric and dysphagic patients of all age groups [3]. Drinking water plays an important role in the swallowing of oral dosage forms. Inconvenience in swallowing tablets can be experienced when water is not available, in cases of motion sickness (kinetosis), sudden episodes of coughing, in allergic conditions and bronchitis. Hence, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention [1].

Fast dissolving tablets (FDTs) are tablets which when placed on the tongue disintegrate rapidly, releasing the drug which dissolves or disperses in the saliva. The faster the drug goes into solution, the quicker the absorption and onset of clinical effect. Fast dissolving tablets are also applicable when local action in the mouth is desired as in the case of local anesthetics for toothaches, mouth sores and teething problems. The fast-dissolving property of the tablets is attributed to quick ingress of water into the tablet matrix resulting in rapid disintegration [2]. The basic approach to the development of FDTs includes the use of superdisintegrants such as cross-linked carboxymethylcellulose (croscarmellose), sodium starch glycolate (Primogel, Explotab) and polyvinylpyrrolidone (Polyplasdone). The addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution, provided the drug is sufficiently water soluble.

Direct compression is the simplest and most cost-effective technique for the manufacture of FDTs. The mixture of drug and excipients to be

*Correspondence may be addressed to E-mail: adenikeokunlola@gmail.com.

compressed must possess good flow properties in order to be directly compressed into tablets without any preliminary treatment. Direct compression method is suitable for the manufacture of tablets of thermolabile and hydro-labile drugs and excipients. This is because fewer unit operations are required and the steps requiring heating and addition of moisture are totally avoided.

Native starches that were traditionally used as disintegrants have largely been replaced by the new class of disintegrants commonly known as superdisintegrants. One such superdisintegrant is sodium starch glycolate (SSG) [4]. Sodium starch glycolate type-A potato is the sodium salt of carboxymethyl ether of potato starch. Starch glycolates may also be derived from rice, wheat or corn. Sodium starch glycolate is used as a pharmaceutical excipient for tablets and capsules. Its mechanism of action is rapid and extensive swelling with minimal gelling. The effect of introducing large hydrophilic carboxymethyl groups is to disrupt the hydrogen bonding within the polymer structure. This allows water to penetrate the molecule. It has been reported that the type of starch, particle size after chemical modification, degree of substitution and cross-linking, and the amount of soluble by-product of the reaction can affect the performance of SSG [5].

It is possible to synthesize sodium starch glycolate from a wide range of native starches. Three tropical starches with high starch content and potential for modification to synthesize superdisintegrants are from banana, cassava and Chinese yam. Banana *(Musa acuminata*, family Musaceae), is a local plant, indigenous to many tropical countries such as Southeast Asia and various countries in Africa including Nigeria and Uganda. Unripe green banana contains about 20–23% starch [6]. Studies have shown the potential of banana starch as disintegrant in pharmaceutical tablets [7, 8]. Another relatively cheap and high yield source of starch that can be comparable to the properties offered by commercial starches such as maize, wheat, sweet potato, and rice is cassava (*Manihot esculenta*, Crantz, Family Euphorbiaceae). About 25% starch can be obtained from mature, good quality tubers of cassava [9]. Adjei *et al*. studied the disintegrant potential of native starches of five new cassava varieties in paracetamol tablet formulations [9]. The tablets containing cassava starches passed the disintegration test ($DT \leq 15$ min) and exhibited faster disintegration times than those containing maize starch BP (British Pharmacopoeia). Chinese yam starch, obtained from *Dioscorea oppositifolia* (Family Dioscoreaceae) has high starch content of > 30% [10, 11]. Studies on the use of Chinese yam starch as an intragranular tablet disintegrant revealed that it produced tablets with higher mechanical strength when compared to corn starch BP and could be further developed for use in commercial tablet formulations [12]. It appears from literature reports that no attempt has been made to study carboxymethylated starches from these three botanical sources with a view to determine their relative efficiency as superdisintegrants in the formulation of FDTs.

Thus, in the present work, starches obtained from banana, cassava and Chinese yam starches were modified by carboxymethylation, characterized and used as superdisintegrants in domperidone FDTs. Direct compression method was used to prepare the tablets and their mechanical strength and release properties assessed in comparison to tablets containing sodium starch glycolate. Domperidone is an anti-dopaminergic used as an anti-emetic. The fast release of domperidone will assure quick onset of action for fast relief from nausea and vomiting. The Taguchi-based design of experiments (DOE) was employed in which two independent variables (superdisintegrant type and superdisintegrant concentration) were analyzed at four levels with crushing strength-friability ratio (CSFR), disintegration time and

time taken for 80% drug release (t_{80}) chosen as the responses. The Taguchi method is a broadly accepted DOE which has proven useful in producing high-quality products at low cost in a relatively short period of time [13]. In a Taguchi designed experiment, noise factors are manipulated to force variability to occur. From the results, optimal control factor settings that make the process or product robust, or resistant to variation from the noise factors, are identified [14].

EXPERIMENTAL

Materials

The materials used included: sodium starch glycolate (S-D Fine Chemicals, India); monochloroacetic acid (Makek Qualikems, India), aspartame (Xian Lyphar Biotech Co., China), dibasic calcium phosphate and magnesium stearate (BDH Chemicals Ltd, Poole England), peppermint oil (Handa Fine Chemicals, UK), talc (Anmol Chemicals, Mumbai, India), and sodium hydroxide (VWR International Ltd, England). Domperidone was obtained from Mahrshee Laboratories Pvt. Ltd., India. Banana (*Musa acuminata*), cassava (*Manihot esculenta*) and Chinese yam (*Dioscorea oppositifolia*) tubers were obtained from local farmers in Ibadan, Nigeria. All other chemicals were of analytical grade.

Extraction of starches

Fresh, unripe fruits of banana, and mature tubers of cassava and Chinese yam were separately washed with distilled water, peeled, washed again and then cut into small pieces. The pieces were milled into a fine paste using a locally-fabricated laboratory hammer mill and the slurry strained through a muslin cloth. The filtrate was left to settle. The supernatant was decanted at 12 h intervals and the starch slurry re-suspended in distilled water. The starch cake was collected after three days and dried in a hot air oven at 50°C for 48 h. The dried mass was pulverized using a laboratory blender and then screened through a 125-µm mesh sieve [8].

Carboxymethylation of starches

Forty grams of the extracted starch was mixed with 400 mL of isopropyl alcohol and 40 mL of aqueous solution of sodium hydroxide (10.5 mol) and the mixture stirred for 10 min. A 1M solution of sodium monochloroacetate (160 mL) was added and the mixture maintained at 30°C for 6 h with stirring. Aqueous acetic acid solution (50% v/v) was added to the resulting mixture with stirring to pH 5. The product was filtered and washed with 80% aqueous ethanol. The carboxymethylated starch was dried at 50°C for 6 h. The dried starch was powdered and its water content determined (4.0% w/w). The dried starch powder was passed through a 100-mesh sieve and then stored in air-tight containers [15, 16].

Degree of substitution

Carboxymethylated starch (0.5 g) was dissolved in 20 mL of 0.2M NaOH. Distilled water (50 mL) was added, the solution transferred into a 100 mL volumetric flask and made up to volume with water. A 25 mL aliquot of the resulting solution was transferred into a flask and diluted by adding 50 mL of distilled water. The excess of NaOH was back-titrated with 0.05M HCl to the phenolphthalein indicator endpoint. The titration was done in triplicate and the mean volume of HCl used determined. A blank titration was also carried out [17]. The degree of substitution was calculated using Equations 1 and 2.

$$DS = \frac{162 \times nCOOH}{(mds - 58) \times nCOOH} \qquad \text{Eqn 1}$$

where 162 = molar mass of anhydrous glucose unit (AGU) g/mol; mds = mass of dried sample; 58 is the molar mass of CH_3COOH.

$$nCOOH = (Vb - V) \times (CHCl \times 4) \quad \text{Eqn 2}$$

Vb = volume of HCl used for titration of blank; V = volume used in titration of sample; C_{HCl} = concentration of HCl; 4 = ratio of total volume of solution to volume taken for titration.

Amylose content

Amylose content of the starches was determined using the colorimetric method [18]. A 100 mg sample was weighed and transferred into a 100 mL volumetric flask, and 1 mL of 95% ethanol and 9 mL of 1N NaOH added. The sample was heated for 10 min in a water bath, cooled and made up to volume with water. A 5 mL portion of the starch solution was then transferred into a 100 mL volumetric flask, 1 mL of 1N acetic acid and 2 mL of iodine solution added and made up to 100 mL with distilled water. The solution was shaken, allowed to stand for 20 min and the absorbance determined at 620 nm.

Scanning electron microscopy

The starches were coated with gold (SC7640 Sputter Coater, Polaron range, Germany). The particle morphology was analyzed using scanning electron microscopy (Hitachi Model S-2460N Japan). Images of samples were taken at 15.0 kV accelerating voltage and magnification of 500.

Particle size

The particle size of the starches was determined using a light microscope (Olympus Research microscope CH20i, Olympus Optical Co., Shinjuku, Japan).

Fourier transform infrared analysis

The starches were analyzed by Fourier transform infrared (FTIR) spectroscopy (FTIR-8400S, Shimadzu, Japan) in transmission mode. Five grams of starch were mixed with potassium bromide (40 mg) and pressed into a disc. Transmission spectrum were recorded using at least 20 scans with 4 cm^{-1} resolution in the 4000–400 cm^{-1} spectral range.

Swelling index

The volume occupied by 5 g of starch powder when poured into a 100 mL measuring glass cylinder was measured (V_o). Starch suspension (5% w/w) was prepared by adding distilled water to the starch powder at room temperature and then shaken for 5 min. The dispersion was allowed to stand for 24 h before the sedimentation volume (V_s) was measured and the swelling capacity calculated as V_s/V_o [19].

Flowability

The flowability of the starches was assessed using the Hausner's ratio and the Carr's index. The Hausner's ratio was determined as the ratio of the initial bulk volume to the tapped volume. The Carr's index (% compressibility) was calculated as shown in Equation 3.

$$\text{Carr's index} = \frac{(Td - Bd)}{Td} \times 100 \quad \text{Eqn 3}$$

Td = tapped density; Bd = bulk density.

Angle of repose

Thirty grams of starch powder were allowed to flow through a funnel, under the force of gravity, to form a conical heap, and the angle of repose calculated using Equation 4. The angle of repose was calculated from a mean of three determinations.

$$Tan\,\theta = \frac{h}{r} \quad \text{Eqn 4}$$

where h is the height of powder and r is the radius of the base of the cone.

Formulation of domperidone tablets

Sixteen batches of domperidone tablets containing SSG (B_1–B_4), carboxymethylated

starches of banana (B_5–B_8), cassava (B_9–B_{12}) and Chinese yam (B_{13}–B_{16}) as superdisintegrants, each at concentrations of 2%, 4%, 6% or 8% w/w, were prepared by direct compression using the formula in Table 1. For each batch, the required amount of domperidone powder, superdisintegrant, aspartame, peppermint oil and dibasic calcium phosphate were blended for 5 min on a Roto mixer (ROTS-200/250 equipment, Whetstone Leicester, England). The talc and magnesium stearate were added and the mixing continued for 1 min. The powder blends were compressed into tablets using Carver hydraulic hand press (Model C, Carver Inc., Menomonee Falls, Wisconsin, USA) at compression pressure of 113.13 Mpa for 30 s. After ejection, the tablets were stored over silica gel for 24 h.

Tablet weight variation and thickness

Twenty tablets were selected at random and their average weight determined within ±1 mg. Using a micrometer screw gauge, the thickness of twenty tablets was measured within 0.01 mm.

Crushing strength

The crushing strength of the tablets was determined at room temperature by diametral compression using a tablet hardness tester (DBK Instruments 400 060 model EH 01, Mumbai, India) [20].

Friability

The percent friability of the tablets was determined using a friabilator (DBK Instruments, model FH 01, Mumbai, India) operated at 25 revolutions per minute (rpm) for 4 min.

Wetting time

A piece of absorbent paper (12 cm × 10.5 cm) was used to line the inside of a Petri dish **(**internal diameter 9 cm). About 6 mL of distilled water was poured into the lined Petri dish. A tablet having amaranth powder on the surface was placed on the paper. The time required to develop red color on the upper surface of the tablet was taken as wetting time.

Water absorption ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 mL of distilled water. A tablet was kept on paper and time required for complete wetting was determined. Then wetted tablet was weighed and percentage of water absorption was determined using Equation 5.

$$R = \frac{Wb - Wa}{Wa} \times 100 \qquad \text{Eqn 5}$$

Where Wa is weight of tablet before water absorption, Wb is weight of tablet after water absorption, and R is water absorption ratio.

Determination of drug content

Ten tablets of each batch were crushed and an amount of powder equivalent to 20 mg of domperidone weighed and dissolved in 100 mL 0.01N HCl. Suitable dilutions were made and UV analysis of drug content carried out at 284 nm using a UV/visible spectrophotometer (Spectrum Lab 752s, Shanghai, China). The content of domperidone was extrapolated from a standard curve prepared using domperidone chemical reference substance at concentration range of 2–10 µg/mL in 0.01N HCl.

Disintegration

The disintegration time of the tablets was determined in distilled water at 37±0.5^{o}C using a disintegration tester (DBK Instrument, model 40 Tda 01, Mumbai, India).

Table 1: Formulations of fast dissolving domperidone tablets

Batch	Carboxymethylated starch (g)		Domperidone (g)	Aspartame (g)	Peppermint oil (mL)	Talc (g)	Magnesium stearate (g)	Dibasic calcium phosphate to (g)
B_1	Sodium starch glycolate (2%w/w)	4.0	20.0	4.0	2.0	4.0	4.0	200
B_2	Sodium starch glycolate (4%w/w)	8.0	20.0	4.0	2.0	4.0	4.0	200
B_3	Sodium starch glycolate (6%w/w)	12.0	20.0	4.0	2.0	4.0	4.0	200
B_4	Sodium starch glycolate (8%w/w)	16.0	20.0	4.0	2.0	4.0	4.0	200
B_5	Banana (2%w/w)	4.0	20.0	4.0	2.0	4.0	4.0	200
B_6	Banana (4%w/w)	8.0	20.0	4.0	2.0	4.0	4.0	200
B_7	Banana (6%w/w)	12.0	20.0	4.0	2.0	4.0	4.0	200
B_8	Banana (8%w/w)	16.0	20.0	4.0	2.0	4.0	4.0	200
B_9	Cassava (2%w/w)	4.0	20.0	4.0	2.0	4.0	4.0	200
B_{10}	Cassava (4%w/w)	8.0	20.0	4.0	2.0	4.0	4.0	200
B_{11}	Cassava (6%w/w)	12.0	20.0	4.0	2.0	4.0	4.0	200
B_{12}	Cassava (8%w/w)	16.0	20.0	4.0	2.0	4.0	4.0	200
B_{13}	Chinese yam (2%w/w)	4.0	20.0	4.0	2.0	4.0	4.0	200
B_{14}	Chinese yam (4%w/w)	8.0	20.0	4.0	2.0	4.0	4.0	200
B_{15}	Chinese yam (6%w/w)	12.0	20.0	4.0	2.0	4.0	4.0	200
B_{16}	Chinese yam (8%w/w)	16.0	20.0	4.0	2.0	4.0	4.0	200

Dissolution

Dissolution test was carried out on the tablets using the USPXX III basket method DBK-Dissolution rate test apparatus Model 001, Mumbai, India) rotated at 100 rpm in 900 mL of 0.1N hydrochloric acid, maintained at 37± 0.5°C. Samples (5 mL) were withdrawn and replaced with equal amounts of fresh medium. The sample was diluted and the amount of domperidone released at each time interval determined at 284 nm on a UV/visible spectrophotometer (Spectrum Lab 752s, Shanghai, China).

Experimental design

In this study, two factors namely, superdisintegrant type (X_1) and superdisintegrant concentration (X_2) were studied at four levels to determine their effects on dependent variables crushing strength-friability ratio (CSFR), disintegration time and t_{80}. A total of sixteen (16) batches were prepared. The factors, independent variables and the levels selected for the study, are given in Table 2. Taguchi method with L_{16} type of robust orthogonal array design was used to optimize the experimental conditions using Minitab 16 Statistical Software (Minitab Inc., Pennsylvania, USA). Unlike conventional statistical experimental designs that determine the optimum condition on the basis of measured values of the characteristic properties, Taguchi's experimental design determine the optimum condition on the basis of the variability of characteristic properties [21].

Table 2: Factors, variables and their levels employed in Taguchi orthogonal array design

Batch	Variable/Level		Factors	
	X_1	X_2	Superdisintegrant type	Superdisintegrant concentration (% w/w)
B_1	1	1	Sodium starch glycolate	2.0
B_2	1	2	Sodium starch glycolate	4.0
B_3	1	3	Sodium starch glycolate	6.0
B_4	1	4	Sodium starch glycolate	8.0
B_5	2	1	Banana	2.0
B_6	2	2	Banana	4.0
B_7	2	3	Banana	6.0
B_8	2	4	Banana	8.0
B_9	3	1	Cassava	2.0
B_{10}	3	2	Cassava	4.0
B_{11}	3	3	Cassava	6.0
B_{12}	3	4	Cassava	8.0
B_{13}	4	1	Chinese yam	2.0
B_{14}	4	2	Chinese yam	4.0
B_{15}	4	3	Chinese yam	6.0
B_{16}	4	4	Chinese yam	8.0

RESULTS AND DISCUSSION

Characterization of native and carboxymethylated starches

Carboxymethylated starches were prepared with degree of substitution (DS) of 0.30±0.02, 0.32±0.01 and 0.33±0.04 for banana, cassava and Chinese yam, respectively. The values represent the amount of carboxymethyl groups which are in the molecular units of the anhydrous glucose [22]. The degree of substitution is defined as the average number of substituents per anhydro glucose unit (AGU). Each AGU contains three hydroxyl groups (C_2, C_3, and C_6) and the DS value lies between zero and three [23].

The scanning electron micrographs (SEM) of the native and carboxymethylated starches are shown in Figure 1. The SEM shows that native banana starch had particles that are oval in shape, the native cassava starch granules had rounded and ovoid shapes while the Chinese yam starches had polygonal shape.

The mean size of the native and modified starches, amylose content, swelling index, angle of repose, densities as well as the flow properties of the starches are presented in Table 3. The ranking of granule size of the starches was banana > cassava > Chinese yam. Starches with finer particles tend to have a higher number of particles per unit weight which is indicative of a higher potential of achieving homogeneity when mixing the substance with active pharmaceutical ingredients [10]. Eruption of starch granules due to modification by carboxymethylation resulted in larger, porous, aggregated granules.

The amylose contents (Table 3) of the modified starches were observed to be significantly lower than those of the native starches ($p < 0.05$). This is due to the destruction of the helical structure during carboxymethylation which result in lower amylose-iodine complex. The swelling index provides evidence of the magnitude of interaction between starch chains within the amorphous and crystalline domains. The swelling of the starches is due mainly to the amylopectin content [24]. However, the process of carboxymethylation destroyed mainly the amylose content. The modified starches had a significantly higher ($p<0.05$**)** swelling index than the native starch. This is because the hydrophilic nature of the carboxymethyl group enhanced water penetration into the starch granules of the carboxymethylated starch resulting in rapid and greater swelling.

The flow properties of the starches were analyzed using angle of repose, Carr's index and Hausner's ratio. A qualitative measure of the cohesiveness or the tendency of powdered materials to flow is the angle of repose. Angles of 30° or below usually indicate that the powder is free flowing. Angles ≥ 40° indicate poor flow. The native starches showed cohesiveness as indicated by the high angle of repose (> 40°). Modification of the native starches by carboxymethylation improved flow. From the values of the bulk and tapped densities, Carr's index and Hausner's ratio were determined. The Carr's index is a measure of flowability and compressibility of a powder. The Hausner's ratio, which is the ratio of tapped density to bulk density, gives an insight to the degree of densification of powders which could occur during tableting. The lower the Carr's index the better the flowability but the poorer the compressibility.

Carr's index values of 5-10, 12-16, 18-21, and 23-28 represent excellent, good, fair and poor flow properties, respectively [25]. The result indicated that native starches had higher compressibility but poor flowability compared to the carboxymethylated forms. This could also be attributed to larger particle size of the modified starches which reduced cohesiveness within their granules. The results of Hausner's

ratio also confirmed that the process of carboxymethylation resulted in improved flowability. The three carboxymethylated starches fulfil the two important attributes of excipients required for a direct compression formula: good flow and good compressibility.

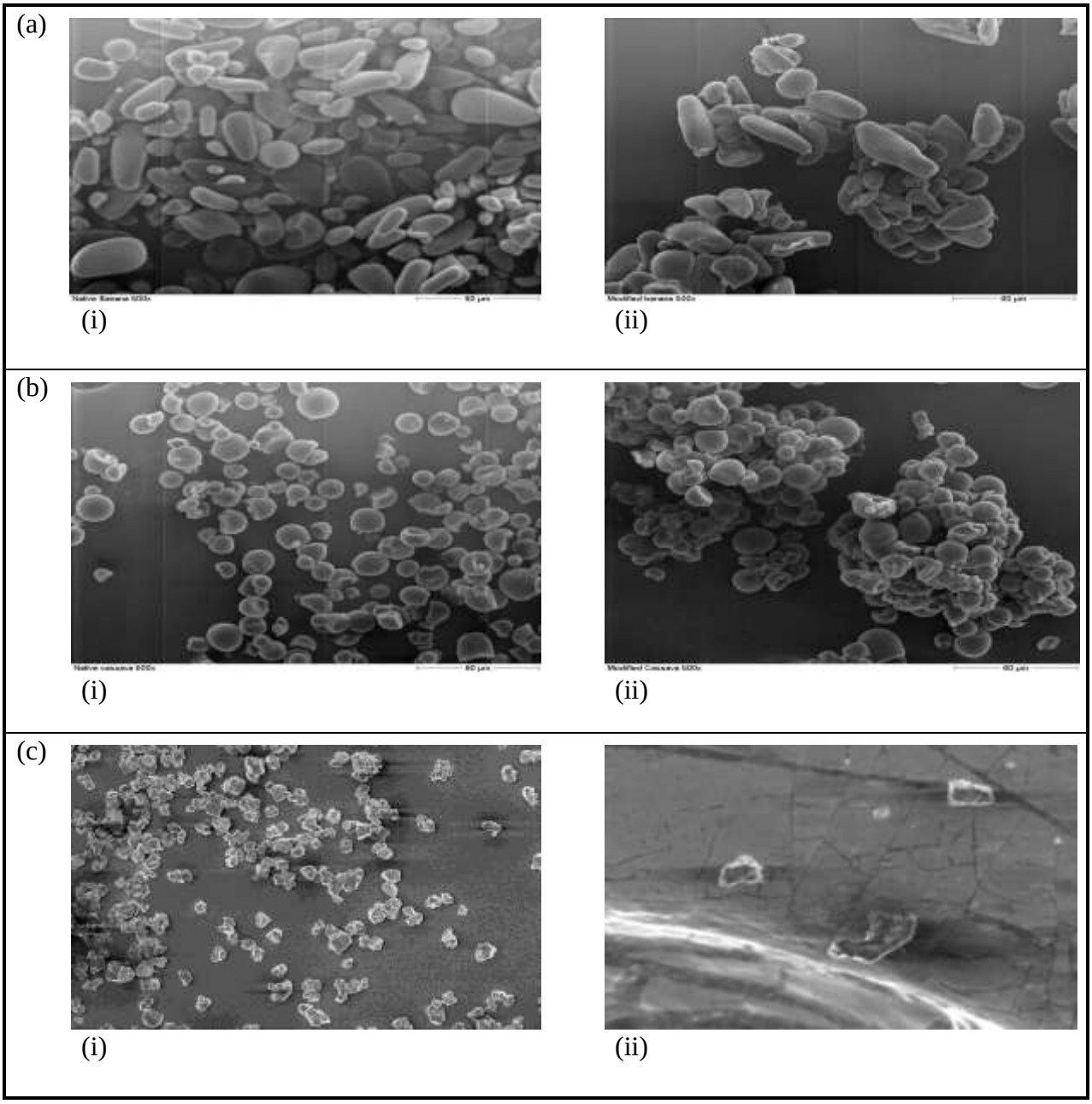

Figure 1: Scanning electron micrographs of (a) banana, (b) cassava and (c) Chinese yam starches in the (i) native and (ii) carboxymethylated forms.

Table 3: Physicochemical properties of native and carboxymethylated starches of banana, cassava and Chinese yam (mean ± sd, n=3

Type of starch	Particle size (μm)	Amylose content (%)	Swelling index	Angle of repose (°)	Particle density (gcm^{-3})	Bulk density (gcm^{-3})	Tapped density (gcm^{-3})	Carr's index (%)	Hausner's ratio
Native banana	30.06±5.55	28.03±0.62	1.10±0.02	48.70±2.12	1.73±0.25	0.56±0.18	0.74±0.28	24.32	1.31
Carboxymethylated banana	60.35±12.20	8.55±0.12	3.30±0.22	24.35±1.70	1.48±0.22	0.51±0.30	0.62±0.25	17.74	1.22
Native cassava	15.5±4.70	22.83±0.37	1.20±0.04	53.43±4.12	1.62±0.10	0.53±0.08	0.77±0.05	24.15	1.45
Carboxymethylated cassava	75.20±10.50	11.56±0.44	2.05±0.30	28.10±2.20	1.59±0.05	0.46±0.03	0.59±0.01	22.03	1.28
Native Chinese yam	7.55±1.10	21.61±0.50	1.10±0.03	56.57±2.22	1.45±0.50	0.45±0.03	0.69±0.02	34.78	1.53
Carboxymethylated Chinese yam	20.35±12.20	11.98±1.27	4.00±0.34	30.08±1.54	1.53±0.10	0.52±0.03	0.40±0.01	23.08	1.30

Table 4: Properties of formulated fast-dissolving domperidone tablets containing carboxymethylated starches (mean ± sd, n=3)

Batch	X_1	X_2 (% w/w)	Weight variation (%)	Wetting time (min)	Water absorption ratio (%)	Crushing strength (N)	Friability (%)	CSFR	Disintegration time (min)	t_{80} (min)
B_1	SSG	2.0	1.15±0.15	1.27±0.65	52.50±4.50	53.29±3.99	0.38±0.02	140.24±.1.95	1.98±0.09	2.70±0.05
B_2	SSG	4.0	1.50±0.11	0.45±0.23	57.00±5.10	42.80±2.30	0.41±0.02	104.39±3.55	1.48±0.05	1.35±0.01
B_3	SSG	6.0	1.90±0.10	0.32±0.25	59.60±1.50	32.95±1.50	0.48±0.04	68.65±2.70	0.94±0.07	1.00±0.00
B_4	SSG	8.0	1.95±0.15	0.27±0.65	62.50±3.20	16.45±0.23	0.50±0.03	32.90±1.45	0.42±0.03	0.50±0.02
B_5	Banana	2.0	1.19±0.07	2.14±0.81	36.16±3.10	101.20±5.65	0.57±0.05	177.54±9.85	2.15±0.10	7.20±0.05
B_6	Banana	4.0	1.20±0.10	2.02±0.50	48.53±2.50	90.55±4.10	0.64±0.03	141.48±8.67	2.07±0.05	5.80±0.07
B_7	Banana	6.0	1.20±0.20	1.52±0.50	58.44±6.20	71.91±3.67	0.68±0.02	105.75±5.54	1.56±0.01	4.45±0.03
B_8	Banana	8.0	1.15±0.15	1.27±0.65	62.50±4.50	54.50±5.09	0.78±0.03	69.87±3.75	1.05±0.02	3.30±0.01
B_9	Cassava	2.0	1.09±0.05	3.20±0.23	84.25±2.24	62.06±6.70	0.29±0.01	214.00±10.00	3.22±0.03	11.60±0.09
B_{10}	Cassava	4.0	1.14±0.20	2.55±0.15	90.10±5.11	58.90±3.65	0.33±0.00	178.48±8.75	2.70±0.01	10.20±0.10
B_{11}	Cassava	6.0	1.20±0.20	1.30±0.03	94.70±7.35	51.38±3.85	0.36±0.01	142.72±7.70	2.20±0.02	8.90±0.06
B_{12}	Cassava	8.0	1.25±0.15	1.18±0.02	96.00±6.60	47.33±4.40	0.44±0.02	107.57±9.99	1.66±0.01	7.70±0.07
B_{13}	Chinese yam	2.0	1.35±0.15	2.73±0.02	90.23±0.05	60.30±6.50	0.24±0.01	251.25±16.32	3.85±0.13	16.00±0.10
B_{14}	Chinese yam	4.0	1.60±0.11	2.16±0.01	96.08±0.08	58.21±7.00	0.27±0.00	215.59±13.88	3.32±0.05	14.70±0.08
B_{15}	Chinese yam	6.0	1.70±0.10	1.68±0.02	98.75±0.06	54.00±5.15	0.30±0.02	180.00±9.57	2.80±0.08	13.50±0.09
B_{16}	Chinese yam	8.0	1.90±0.15	1.08±0.65	99.50±3.20	50.70±4.90	0.35±0.01	144.86±8.86	2.30±0.11	12.10±0.06

SSG = Sodium starch glycolate.

The FTIR spectra of the native and carboxymethylated starches are presented in Figure 2. The percentage transmittance was plotted versus the wavelength. The vibration band of α-1,4-glycosidic linkage (C-O-C) at 926 cm^{-1}, the stretching band of primary alcohol (-CH_2OH) at 1078 cm^{-1} and the water adsorbed in the amorphous regions at 1641 cm^{-1} are the characteristic groups of native starches. Substitution of carboxymethyl group on the three starches can be identified with the presence of some peaks ranging between 1300 and 860 cm^{-1}, which are attributed to the stretching vibrations of C-O in C-O-C and C-O-H from glycosidic molecules. The presence of carboxymethyl group can be identified as the peak around 1400 cm^{-1} and around 1600 cm^{-1} attributed to the unsymmetrical and symmetrical stretching vibrations of the COO- functional group [24]. The peaks detected at 1411 cm^{-1} and 1344 cm^{-1} correspond to $–CH_2$ scissoring and –OH bending. Those peaks did not appear in the native starches. The reduced intensity of the absorption band around 3600 cm^{-1}, due to OH stretching, imply that some OH groups were carboxymethylated.

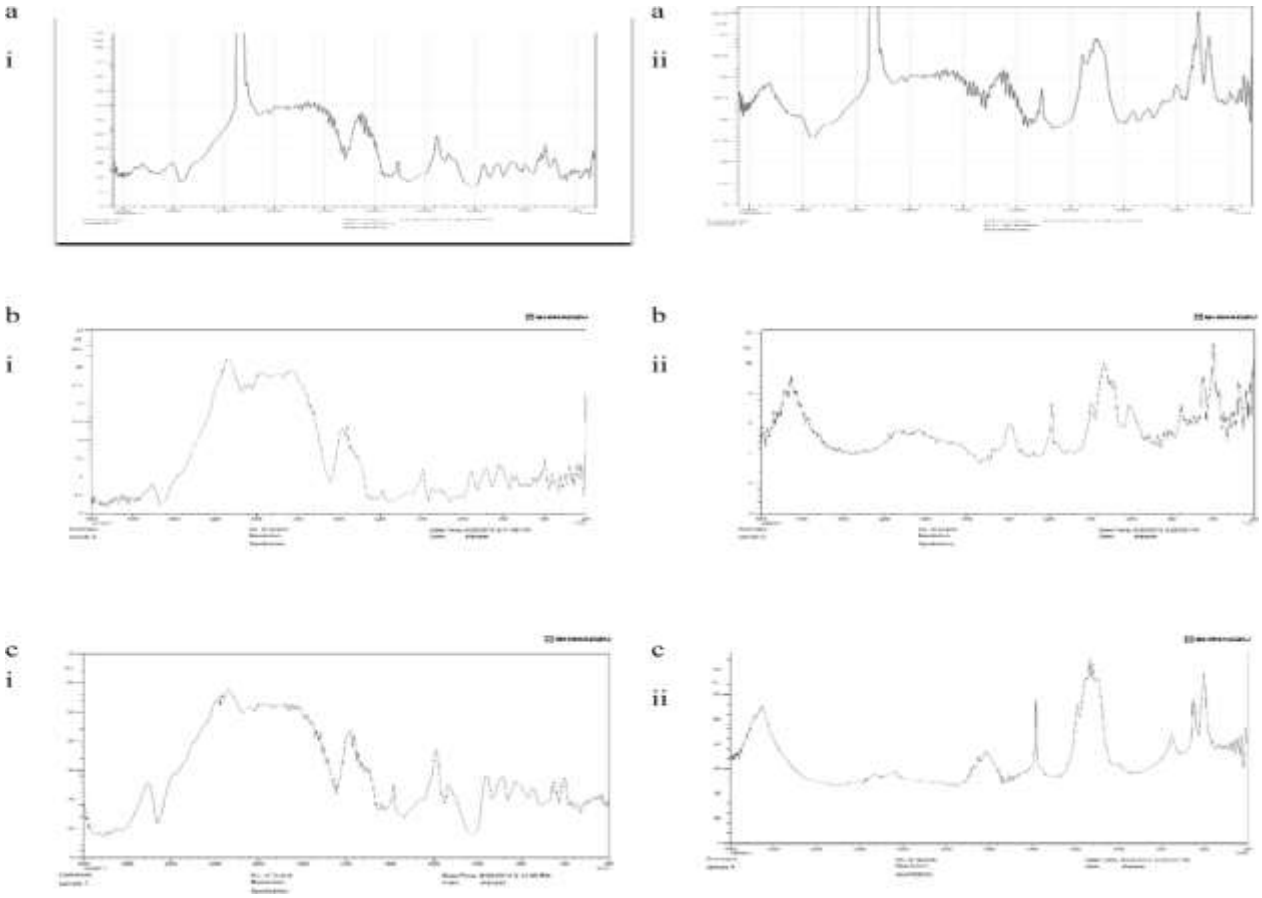

Figure 2: Fourier-transform infrared spectra of (a) banana, (b) cassava and (c) Chinese yam starches in (i) native and (ii) carboxymethylated forms.

Characterization of domperidone tablets

Some key parameters to be considered in formulating FDTs are taste and disintegration time. To evaluate the efficiency of the carboxymethylated starches as superdisintegrants in fast-dissolving domperidone tablets, the standard SSG and the carboxymethylated starches were each used at concentrations of 2%, 4%, 6% and 8% w/w.

Dibasic calcium phosphate was used as direct compression filler because it has no intrinsic disintegrant property. Aspartame and peppermint flavour were used as sweetening and flavouring agents, respectively, to enhance taste and improve mouth feel while talc and magnesium stearate were used as the flow aid and lubricant, respectively. The results of tablet weight variation, wetting time, water absorption ratio, crushing strength, friability, crushing strength-friability ratio, disintegration time and dissolution time (t_{80}) are presented in Table 4.

All the formulated tablets complied with the weight variation test as the % weight variation was within the ±7.5% International Pharmacopoeial limits [26]. The wetting time was observed to reduce with increase in superdisintegrant concentration. Generally, at all concentrations, the ranking of wetting time was Chinese yam > cassava > banana > SSG, showing that the wetting time was faster for tablets containing SSG than those containing the modified starches. Wetting time is an important parameter for FDT formulations and it provides information on wetting lag time before disintegration [4]. The faster wetting time observed for tablets containing SSG may be due to its rapid water-absorbing nature involving both capillary and swelling mechanisms [27]. The experiment on wetting absorption ratio was done to mimic the action of saliva in contact with tablet. The ranking of the water absorption ratio was similar to that of the wetting time showing that the modified starches had higher ratios than SSG. The water absorption ratio of the tablets was also observed to increase with increase in superdisintegrant concentrations due to enhanced water uptake capacity of the superdisintegrants as the proportion increased [28].

All tablets containing modified starches were of higher mechanical strength ($p < 0.05$) than those containing SSG. With increase in concentration of superdisintegrant, tablet crushing strength decreased while friability increased. All the tablets passed the United States Pharmacopeia (USP) specifications for friability of uncoated tablets, i.e., <1% w/w [29]. For the modified starches, only domperidone tablets containing carboxymethylated banana starch had higher friability than those containing SSG. Crushing strength and friability of tablets serve as criteria to guide product development and as quality control specifications. Tablets must be able to withstand the rigours of handling and transportation experienced in the manufacturing plant, in the drug distribution system, and in the field at the hands of the end users. The crushing strength-friability ratio (CSFR) was calculated using the values of crushing strength and friability. The CSFR has been reported to provide a better parameter for measuring tablet strength [30]. Higher values of CSFR imply stronger tablets. Generally, the ranking of CSFR was Chinese yam > cassava > banana > SSG, with the carboxymethylated starches showing significantly higher values of CSFR ($p < 0.001$) than those of SSG at all concentrations.

Swelling is one of the major mechanisms by which starches impart their disintegrating effect, causing the tablet to break apart. Modification of starches by carboxymethylation led to enhanced hydration and swelling capacity of the starches. The values of disintegration time (DT) were found to be in the range of 0.42±0.03 to 3.85±0.13 min and the ranking was generally Chinese yam > cassava > banana > SSG. Disintegration time was observed to reduce with increase in concentration of superdisintegrant. The higher the amount of starch disintegrant exposed to the disintegrating fluid, the higher the amount of water absorbed producing higher swelling force that will facilitate disintegration [31]. The values of t_{80} were obtained from the release profiles of the various formulations. The ranking of t_{80} was similar to those of DT with SSG having the fastest release. The longer release times of the tablets containing the modified starches could be related to their

higher mechanical strength since bonding strength can retard liquid penetration into the interstitial void spaces of the tablets, thereby reducing swelling of the disintegrant and prolonging disintegration [32]. It was also observed that as the concentration of superdisintegrants increased, dissolution time decreased.

Experimental design

Taguchi method was chosen for the design of the experiments and analysis of results, and not a full factorial design that will require numerous experiments to be carried out, rendering it laborious and complex when the number of factors increases. The L_{16} orthogonal array, a design of 2 factors at 4 levels, was considered; sixteen (16) experiments were required for the study [13]. Taguchi design analysis was carried out using Signal to Noise Ratio (SNR) to analyze and identify the factor that significantly affected the response as well as the contribution of each factor. Analysis of Variance (ANOVA) was then carried out to determine the relative effect of each factor on the responses [14, 33].

The SNR graphs of the factor levels are shown in Figure 3. There are three types of SNR criteria for optimization and these are referred to as smaller-the-better; larger-the-better and nominal-the-best. To get the best performance for the FDTs, higher CSFR but lower DT and t_{80} values are desired. Hence, the higher-the-better criteria was selected for CSFR while the smaller-the-better criteria was selected for DT and t_{80}. The S/N ratio (Y axis) was plotted vs values representing the levels of the process parameters (X axis). The more significant factor can be determined by the larger difference of S/N ratio. As observed from the SNR graph, the factor X_1 (superdisintegrant type), represented as 'A', had a greater influence on CSFR and $t_{80;}$ this is indicated by the larger difference of S/N ratio. This result suggests that superdisintegrant type is a significant parameter that can increase mechanical strength (CSFR) and t_{80} as the type of superdisintegrant is changed from level 1 to 4, i.e., from SSG (Level 1) to the modified starches with the values increasing from banana (Level 2) to cassava (Level 3). Changing the superdisintegrant type to Chinese yam (Level 4) gave the highest value. On the other hand, the factor X_2 (superdisintegrant concentration), represented as 'B', had more influence on DT with changes in the concentration from 2 to 4% w/w (Levels 1 to 2) or from 4 to 6% w/w (Level 3) resulting in lower values of DT. Changing the concentration from 6 to 8% w/w gave the fastest disintegration time for each superdisintegrant used.

Table 5 shows the direct effect of each factor at the desired level which was investigated using means analysis while its response was determined as delta parameter. Delta parameter measures the size of the effect by determining the average of the difference between the highest and lowest characteristic for a factor. The ranking of the delta values showed that superdisintegrant type (X_1) had the greater effect on CSFR and t_{80} while X_2 (superdisintegrant concentration) had the greater influence on DT. The results of ANOVA are presented in Table 6. Fischer test values (F-value) show the influence of the controlling factors over CSFR, DT and t_{80} in these formulations. Usually, if F-value is greater than 4, it means that the control factor has a huge impact on the quality attribute. The F-value for superdisintegrant type (X_1) was higher for CSFR and t_{80}. On the other hand, F-value for superdisintegrant concentration (X_2) was higher for DT. The *p*-value <0.05 confirmed the significance of the influence of these factors.

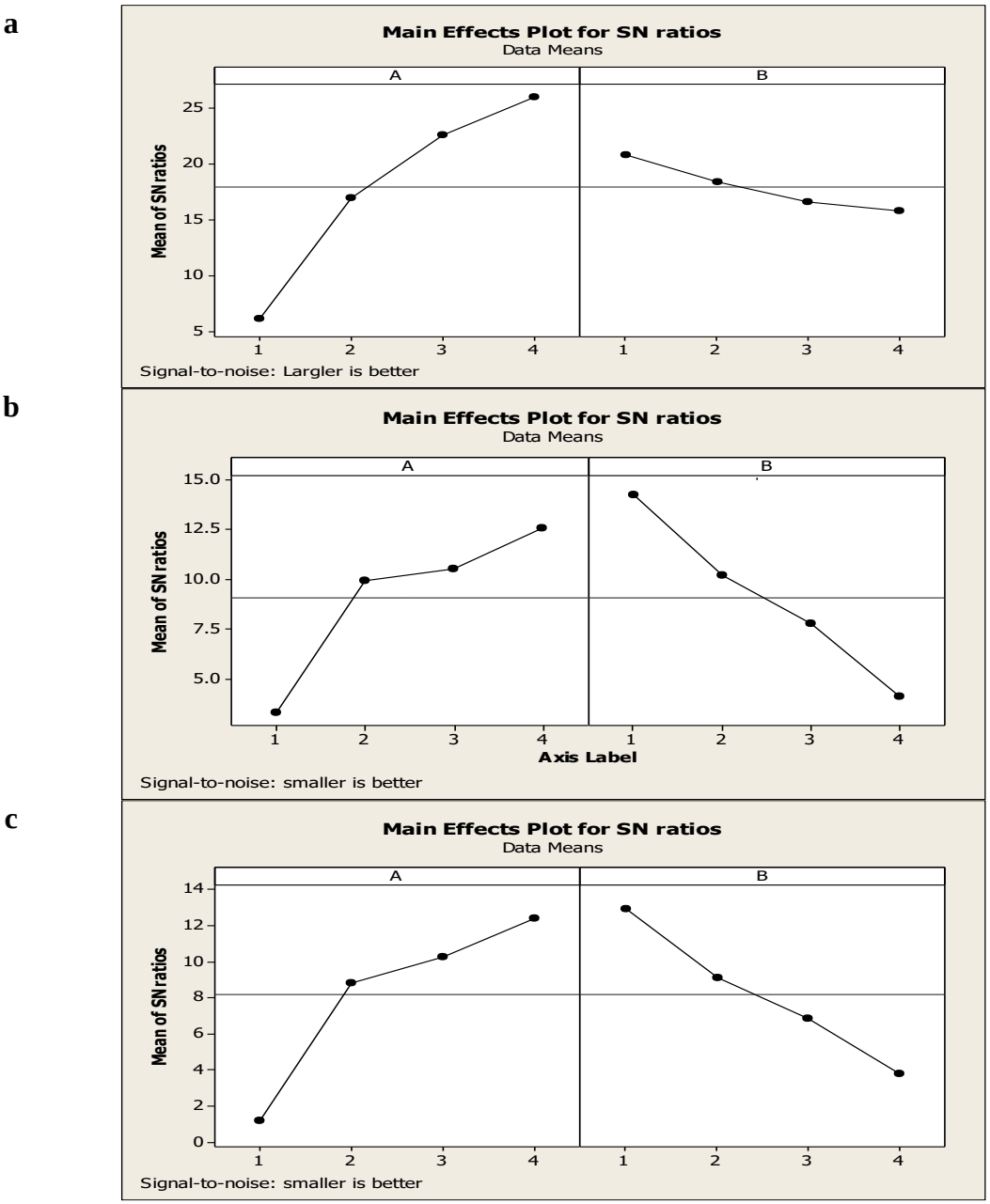

Figure 3: Analysis of signal-to-noise ratio graph by (a) CSFR; (b) DT; and (c) t_{80} versus A (superdisintegrant type) and B (superdisintegrant concentration).

Optimization of formulation

In order to verify the optimization of the formulations using the Taguchi method, confirmation experiments were carried out after determining the levels of the variables that would give the optimal results [34]. The results of the confirmation experiments for CSFR, DT and t_{80} were obtained at the optimum variable levels. As determined in Figure 3, the factors and the levels A_4B_1 were used for the calculation of the predicted optimal value of CSFR while A_1B_4 were used for the calculation of the predicted optimal values of both DT and t_{80}. This suggests that Batch B_{13} with Chinese yam starch as superdisintegrant at 2% w/w was the optimum formulation in terms of highest CSFR value while Batch B_4 containing SSG at 8% w/w

was the optimum formulation for fast release showing low values of DT and t_{80}. Based on these optimized results, two new formulations were made under the derived optimal conditions according to Taguchi method. The percent prediction error (% PE) was calculated and the results are presented in Table 7. It was observed that the predicted values are in close agreement with the observed values confirming the reliability of the Taguchi-based DOE.

Table 5: Response table for means

Response	Level	X_1	X_2
CSFR	1	86.54	195.76
	2	123.66	159.99
	3	160.69	124.28
	4	197.93	88.80
	Delta	111.38	106.96
	Rank	1	2
DT	1	1.205	4.050
	2	2.958	2.393
	3	2.445	1.875
	4	3.067	1.357
	Delta	1.862	2.693
	Rank	2	1
t_{80}	1	1.563	9.375
	2	5.188	8.012
	3	9.600	6.963
	4	14.075	6.075
	Delta	12.513	3.300
	Rank	1	2

CSFR = crushing strength-friability ratio; DT = disintegration time.

Table 6: Analysis of variance

Response	Source	DF	Seq SS	Adj SS	Adj MS	F	P
CSFR	A	3	27553.8	27553.8	9184.6	124667.41	0.000
	B	3	25429.6	25429.6	8476.5	115056.27	0.000
	Residual Error	9	0.7	0.7	0.1		
		15	52984.1				
DT	A	3	8.740	8.740	2.913	2.25	0.152
	B	3	16.334	16.334	5.445	4.20	0.041
	Residual Error	9	11.663	11.663	1.296		
		15	36.738				
t_{80}	A	3	352.788	352.788	117.596	366.50	0.000
	B	3	24.211	24.211	8.070	25.08	0.000
	Residual Error	9	2.996	2.896	0.322		
		15	379.894				

CSFR = crushing strength-friability ratio; DT = disintegration time.

Table 7: Predicted and observed values of checkpoint batches

Factor	CSFR		DT		t_{80}	
	Level	Value	Level	Value	Level	Value
Superdisintegrant type	4	Chinese yam	1	SSG	1	SSG
Superdisintegrant concentration	1	2% w/w	4	8% w/w	4	8% w/w
Predicted value		251.37		0.368		0.359
Observed value		251.25		0.380		0.370
% Error		-0.05		+3.16		+2.97

CSFR = crushing strength-friability ratio; DT = disintegration time; SSG = Sodium starch glycolate.

CONCLUSION

This study has shown that fast dissolving tablets of domperidone can be prepared by the use of the carboxymethylated starches obtained from three tropical crops, banana, cassava and Chinese yam. The results of Taguchi design revealed that superdisintegrant type was the most significant parameter to influence CSFR and t_{80} while superdisintegrant concentration was the more significant for DT. Optimal formulations with highest CSFR value and lowest DT and t_{80} values were formulations of domperidone tablets containing carboxymethylated Chinese yam starch at 2% w/w and those containing standard SSG at 8% w/w. At appropriate concentration, carboxymethylated starches of banana, cassava and Chinese yam can be utilized as superdisintegrants in pharmaceutical tablet formulations. These results are promising but further investigations are necessary to explore their efficacy at other concentrations to optimize their use as superdisintegrants in various pharmaceutical tablet applications.

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