Optimization of formulations of chloroquine phosphate tablets containing Ofada rice (*Oryza glaberrina*) starch as a binder: a Taguchi based grey-relational design

Adenike Okunlola*

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

Received: June 21, 2020; *Accepted:* September 5, 2020

Original Article

ABSTRACT

Chloroquine phosphate (CP) is an antimalarial drug that was popular for its fast onset of action, safety in all trimesters of pregnancy, and its beneficial effects in rheumatoid arthritis and lupus erythematosus. CP has poor tableting properties and therefore requires a binder, among other excipients, to form robust tablets. The potential of using Ofada rice (*Oryza glaberrina* Steud) starch as the binder in tablet formulations of CP was compared to B.P. grade established corn starch. The starches were characterized for morphology (Scanning electron microscopy, SEM), crystallinity (Fourier Transform Infra-Red Spectroscopy, FTIR), swelling, densities, flow, and compressing properties. CP tablets containing the native starches as binders at 5.0 and 10.0% w/w respectively were prepared using wet granulation at compression pressures 56.56 and 113.13 MNm^{-2} for a period of 15 and 30 seconds. The potential of using Ofada rice starch as a binder was examined using the Taguchi based grey-relational design (L-16 orthogonal array). Binder type, binder concentration, compression pressure, and compression time were the four input parameters used at two levels, while the crushing strength-friability-disintegration time ratio (CSFR/DT) and t_{80} were the responses. Grey relational coefficients and grey relational grades were determined to identify the optimal levels of the input parameters. Ofada rice starch had smaller particles, higher swelling, and better compressibility. For the CP tablet formulations, the Ofada rice starch showed greater CSFR/DT values and dissolution times. The Taguchi based grey-relational analysis showed that binder concentration was the most significant individual parameter that influenced both responses while the interaction between binder type and binder concentration had the highest influence. The optimum parameter levels for CSFR/DT and t_{80} were CP tablets containing Ofada starch at 5.0% w/w concentration, compressed at 56.56 MNm^{-2} for 15 seconds. Ofada rice starch shows potential as a binder in tablet formulations.

KEY WORDS: Chloroquine phosphate tablets, dissolution time, Taguchi based grey-relational design, mechanical properties, *Oryza glaberrina* starch, excipients

INTRODUCTION

Chloroquine phosphate (CP) is an antimalarial and amoebicides, active against erythrocytic forms of *Plasmodium vivax*, *Plasmodium ovale*, and sensitive strains of *Plasmodium falciparum*. CP remains one of the most popular antimalarial medicines because of its fast onset of action and its safety in all trimesters of pregnancy (1). Chloroquine phosphate may also be used for the treatment of rheumatoid arthritis and lupus erythematosus for extended periods although its use

*Corresponding address: Adenike Okunlola, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, University of Ibadan, Ibadan, Nigeria,
E-mail: adenikeokunlola@gmail.com, a.okunlola@mail.ui.edu.ng
Tel: 234 8023351064

for such is limited because of its possible toxic effects on eye and hair pigments. Its use as an antimalarial is also declining because it has become resistant to Plasmodium strains (2). CP was chosen as the drug of choice for this study because it has poor tableting properties requiring a binder among other excipients to form robust tablets.

Binders provide the necessary bonding to hold powders in a drug formulation. For solid dosage forms, a better understanding of the fundamental properties of binders helps in developing better formulations and products. Starches are important excipients used as binders in tablet formulations. Rice is one of the most important crops in Nigeria and its production represents a significant part of the government strategy to overcome food shortage and improve self-sufficiency for both local consumption and export. Ofada is a generic name used to describe rice cultivated and processed in a group of communities in the Ogun state and some rice-producing clusters in South West Nigeria. Ofada rice contains a high amount of starch (3). A literature review reveals that no attempt has been made before to study Ofada rice starch to determine its relative efficiency as a binder in tablet formulations. Thus, this study was designed to evaluate the potential of Ofada rice starch as a binder in chloroquine phosphate tablet formulations using the Taguchi based grey-relational design. The conventional Taguchi method can effectively establish optimal parameter settings for single performance characteristics but becomes unsuitable when multiple performance characteristics with conflicting goals are considered (4). The Taguchi based grey-relational design is a new method used to solve multi-response optimization problems (5). The parameter design of the method utilizes orthogonal array (OA), signal-to-noise (S/N) ratios, main effects, and analysis of variance (ANOVA)(6, 7). The four input parameters in this study were binder type, binder concentration, compression pressure, compression time at two levels while the responses were crushing strength-friability-disintegration ratio (CSFR/DT) and dissolution time, t_{80}.

MATERIALS AND METHODS

Materials

Chloroquine phosphate BP and corn starch BP were obtained from BDH Chemicals Ltd., Poole, UK, lactose from DMV Veghel, Netherlands, and the Ofada rice was obtained from farmers in Sagbon, Ogun State, Nigeria.

The extraction of the starch

The starch was extracted from the Ofada rice grains by soaking them in distilled water. The mixture was blended to make a slurry that was then strained through a muslin cloth followed by allowing the filtrate to settle. The supernatant was decanted at 12 hours intervals and the starch slurry resuspended in distilled water. The starch cake was collected after 72 hours and dried in a hot air oven at 50°C for 48 hours. The dried mass was pulverized and then screened through a sieve of size 250 micrometers (8).

Characterization of starch

Morphology

The shape of the starch granules was examined using a scanning electron microscope (Hitachi SU8030 FE-SEM Tokyo, Japan) at an accelerating potential of 5.0 Kv. All samples were sputter-coated with Au/Pd prior to examination. The size of the starch granules was examined using an optical microscope (Olympus Optical Co, Japan).

FT-IR Analysis

The corn and Ofada starch powders were analyzed by FT-IR (FT-IR Thermo Nicolet Nexus 870 Madison, WI, USA) in transmission mode. Transmission spectra were recorded using at least 64 scans with $8cm^{-1}$ resolution in the spectral range 4000-400 cm^{-1}.

Swelling index

The swellability of both starches was determined at room temperature (25°C±2°C) using a modification

of the method described previously by Bowen and Vadino (9). The starch powder (5 g) was placed into a 100 mL measuring cylinder and the volume was determined (V_1). Distilled water (90ml) was added and the dispersion was shaken for two minutes and then made up to 100 ml in volume by adding more distilled water. The slurry was allowed to stand for 24 hours before the sedimentation volume was read (V_2). The swelling index was calculated as V_2/V_1.

Particle density

A 50-mL capacity pycnometer was weighed empty (W), filled with the non-solvent (xylene) and the excess wiped off. The weight of the pycnometer with the non-solvent was determined (W_1). The difference in weight was calculated as W_2. A 2 g quantity of each starch was weighed (W_3) and quantitatively transferred into the pycnometer bottle. The excess non-solvent was wiped off and the pycnometer was weighed again (W_4). The particle density was calculated using Equation 1:

$$\frac{W_2 W_3}{50(W_3 - W_4 + W_2 + W)} gsm^{-3} \quad \text{Eq. 1}$$

Bulk density

The bulk density of each starch powder at zero pressure (loose density) was determined by pouring 10 g of the powder at an angle of 45° through a funnel into a 50 mL cylinder and noting the volume occupied by the powder.

Tapped density

The tapped density was measured by applying 100 taps to 10 g starch inside a graduated cylinder at a standardized rate of 38 taps per minute from a height of 2.54 cm.

Flowability

The flowability of the starches was assessed using Carr's index and the Hausner ratio using Equations 2 and 3, respectively.

$$Carr's\ index = \frac{(Tapped\ density - Bulk\ density)}{Tapped\ density} x100 \quad \text{Eq. 2}$$

$$Hausner\ ratio = \frac{Tapped\ density}{Bulk\ density} \quad \text{Eq. 3}$$

Angle of repose

Starch powder (5 g) was allowed to flow freely through a funnel under gravity, to form a conical heap. The angle of repose was calculated using Equation 4:

$$\text{Tan}\,\theta = \frac{Height}{Radius} \quad \text{Eq. 4}$$

Where, height refers to the height of the powder and radius refers to the radius at the base of the cone.

Studies of compressional behavior using the Kawakita model

Quantities (500 mg) of starch powder mixed with 0.5% w/w magnesium stearate were compressed into tablets at predetermined loads on a tableting machine (Korsch XPI KOO10250, Berlin, Germany) using a 10 mm die with flat-faced punches. After ejection, the tablets were stored over silica gel for 24 hours to allow for elastic recovery and hardening. The weights (w) and dimensions of the tablets were then determined within ± 1mg and 0.01 mm, respectively.

The Kawakita compression equation was used to assess the compaction properties of the starches (10). The reduction in the volume of starch powders due to compression was evaluated using Equation 5.

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \quad \text{Eq. 5}$$

Where, P is the compression pressure and both a and b are constants that can be used to estimate the flow and cohesive properties of powders. Constant a describes the compressibility while the reciprocal of constant b describes the cohesive properties of powders. The term C describes the volume reduction during compression and was calculated using Equation 6:

$$C = \frac{V_0 - V}{V_0} \quad \text{Eq. 6}$$

Where, V_0 is the loose or bulk volume of the starch powder and V is the volume of the powder after the application of pressure.

Preparation of the granules for the chloroquine phosphate formulations

Batches (100 g) of a basic formulation of chloroquine phosphate (50% w/w) where corn starch was included as a disintegrant (10% w/w) and lactose included as a diluent (at a sufficient quantity to make up 100 g) were dry mixed for 5 minutes using a ceramic mortar. The starch powders (Ofada or corn at 5.0 and 10% w/w) were mixed with approximately 20 mL of distilled water and heated on a water bath to form a starch paste. This was added to the powder blend in the mortar to produce granules containing different concentrations of Ofada rice and corn starches as the binder. Massing was continued for 5 minutes and the wet masses were granulated by passing them manually through a mesh 12 sieve (1400 microns). They were then dried in a hot air oven at 50°C for 18 hours. The dried granules were sieved through a mesh 16 sieve (1000 microns) and then stored in airtight containers.

Compression of granules into tablets

The CP granules (500 mg) were compressed lightly using a predetermined load (56.56 and 113.13 MNm^2) on a Carver hydraulic press (Model C, Carver Inc. Menomonee Falls, WI) using a 10.5mm die and flat-faced punch for 15 and 30 seconds to form tablets.

Evaluation of the chloroquine phosphate tablets

Tablet weight and thickness

Twenty tablets were selected at random and their average weight was determined within ±1 mg (Mettler PC 440 Delta range®, CH-8606 Greifensee-Zurich, Switzerland). Using a micrometer screw gauge, the thickness of the twenty tablets was measured within ± 0.01 mm.

Hardness test

The crushing strength of the tablets was determined at room temperature by diametral compression with a hardness tester (11). The results were taken only from tablets which split cleanly into two halves without any sign of lamination.

Friability testing

The percent friability of the tablets was determined using a friability tester operated at 25 RPM for 4 minutes.

Disintegration test

The disintegration time of the tablets was determined in distilled water at 37°C ±0.5°C using a disintegration tester. Determinations were carried out in triplicate.

Assay of drug content

Five tablets were crushed and dissolved in a phosphate buffer and filtered. The amount of chloroquine phosphate in the solution was determined using a UV spectrophotometer at a wavelength of 343 nm.

Dissolution test

Dissolution tests were carried out on the tablets using the the USPXX III basket method rotated at 100 RPM in 900 ml of 0.1M HCl, and maintained at 37°C ± 0.5°C. Samples (5 ml) were withdrawn and replaced with equal amounts of fresh medium. The sample was diluted and the amount of chloroquine phosphate released was determined using a UV visible spectrophotometer at a wavelength of 343 nm.

Experimental design

The impact of four input parameters: binder type, binder concentration, compression pressure, and compression time, selected at two levels, and their interactions were studied using a L-16 orthogonal array design using the MINITAB 16 statistical

software (Minitab, USA). A total of 16 batches were formulated for the experiment. The Taguchi design of experiment was used for the selection of control factors that influence the mechanical and release properties in the tablets formulations of chloroquine phosphate (CSFR/DT and t_{80}). The least variation and the optimal parameters in the Taguchi method were obtained by means of using a S/N ratio. The greater the S/N ratio, the more stable the quality achieved (12). A Taguchi based grey-relational design was used to determine the optimal parameters for the formulations. The entire performance characteristics desired for CSFR/DT and t_{80} were combined into a single value that can be used as a single characteristic for optimization. This was achieved by normalizing the performance characteristics for the process referred to as Grey relational generation (GRG). In the Grey relational analysis, a linear normalization of the experimental results was performed in the range of 0 and 1. The normalized data were used to calculate the deviation sequence (quality loss estimate) (4). The Grey relational coefficient was then calculated to express the relationship between the ideal and actual normalized experimental results. From the mean values of the Grey relational coefficient, the Grey relational grade was obtained, thus converting the multi-objective optimization into a single optimization. The S/N ratio plot for the Grey relational grade was calculated using MINITAB 16 software. The greater the value of the Grey relational grade, the closer the corresponding factor combination is to the optimal (5). Based on the Grey relational grade, the effects of the factors were estimated and the optimal level for each controllable factor was determined. The main effect plots were used to determine the optimum factor levels for each response. Analysis of variance (ANOVA) was then used to determine the relative influence of each input parameter. In the ANOVA analysis, the sum of squares and variance were calculated. F-test value at 95% confidence level was used to determine the significant factors.

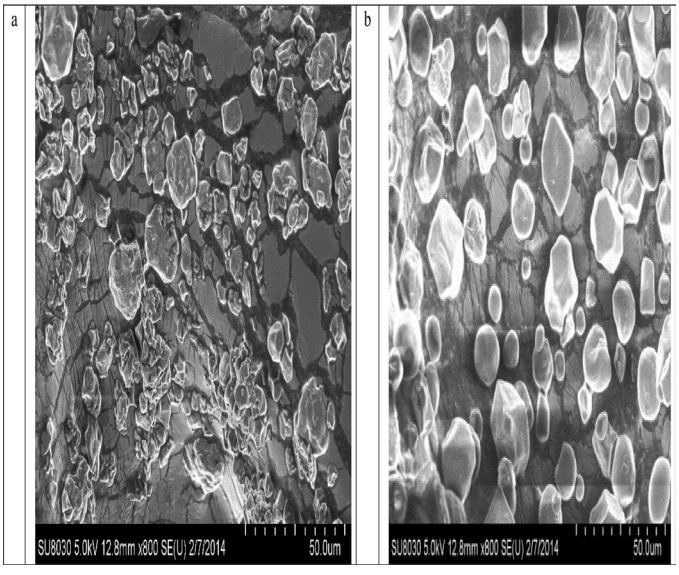

Figure 1 Scanning electron micrographs of (a) native Ofada rice and (b) corn starch Mg x 800

RESULTS AND DISCUSSIONS

Starch yield and morphology

The yield of Ofada rice starch was 42% dry weight. The Scanning Electron Micrographs (SEM) of native Ofada rice and corn starches are shown in Figure 1. The SEMs show that Ofada rice starch granules were polygonal in shape. Corn starch on the other hand had granules that were angular and polyhedral in shape. Particle shape can influence compaction characteristics as it affects the packing behavior of the starches. This is because there is a tendency for particle rearrangement to occur in the initial stages of the compaction process (13). The granule sizes of the starches are presented in Table 1. The starch granules of the Ofada rice were smaller than those of corn. Starches with finer particles tend to have a higher number of particles per unit weight which is indicative of a greater potential for achieving homogeneity when mixing the it with an active pharmaceutical ingredient (14).

Fourier Transform Infra-red (FT-IR) analysis

The FT-IR spectra of the native corn and Ofada rice starches are shown in Figure 2. The spectra revealed characteristic absorption at 992, 929, 861, 765, and 575 cm^{-1}. The bands are due to the entire anhydroglucose rings stretching vibrations. The FT-IR band at 1042 cm^{-1} was present. Broad bands observed at 3000 – 3600 cm^{-1} corresponding to OH stretching while the peaks at 2950 cm^{-1} and 1647cm^{-1} correspond

Table 1 Material and compression properties of native Ofada rice and corn starches (mean ± sd, n = 3)

STARCH	PARTICLE SHAPE	PARTICLE SIZE µm	SWELLING POWER	TRUE DENSITY gcm^{-3}	BULK DENSITY gcm^{-3}	TAPPED DENSITY gcm^{-3}	HAUSNER RATIO	CARR`S INDEX	ANGLE OF REPOSE °	KAWAKITA Di (1 - a)	KAWAKITA Pk (1/b)
Ofada rice	Polygonal	2.20±0.05	2.25±0.10	1.53±0.04	0.63±0.01	0.82±0.01	1.30±0.04	23.89±0.02	39.40±0.50	0.392	8.78
Corn	Polyhedral, angular	14.60±1.10	1.20±0.04	1.49±0.02	0.47±0.01	0.60±0.01	1.28±0.01	21.67±1.40	51.80±1.38	0.355	2.50

to C-H stretching and O-H bending respectively.

FTIR was the only analytical technique used to determine chemical equivalency due to resource limitations even though other techniques would have been better in establishing comparisons and differences between the two starches.

Densities of starches

The figures of the particle, bulk, and tapped densities for the starches are presented in Table 1. The properties of the starches influence the various aspects of powder processing such as milling, blending, flow from hoppers, and compression in the die. The density of a powder describes its packing behavior. The values for the particle, bulk, and tapped densities of the Ofada starch were greater than those of the corn starch. The bulk density of a powder describes its packing behavior. Greater bulk density is advantageous in tableting because of a reduction in the fill volume of the die. The tapped density indicates the rate and extent of packing that would be experienced by a material during the various unit operations of tableting (13). The tapped density of Ofada rice starch was greater than that of the corn. The difference observed in the densities between Ofada and corn could be due to the difference in particle shape and particle size distribution, both of which affect the packing arrangement of particles.

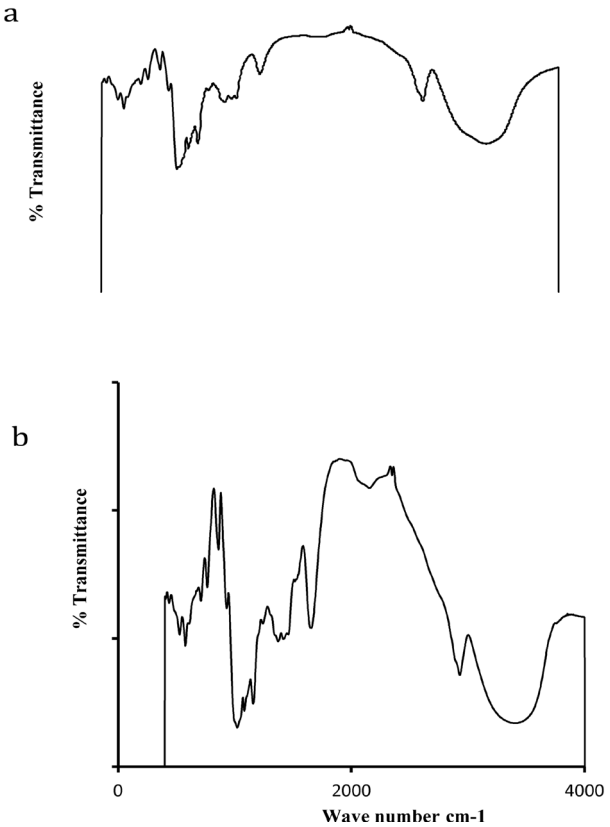

Figure 2 FTIR spectra of (a) native corn starch and (b) native Ofada rice starch

Flow properties of starches

The values of Carr's index, Hausner ratio, and angle of repose are also presented in Table 1. Carr's index is a measure of the flowability and compressibility of a powder. The lower the Carr's index the better the flowability but the poorer the compressibility. The results showed that the Ofada starch had greater compressibility than corn starch (15).

The Hausner ratio (tap to bulk density) indicates the degree of densification which could result from the vibration of the feed hopper, for example, during tableting. Greater values of the Hausner ratio predict significant densification. The Hausner ratio for the Ofada rice starch was greater than that of the corn starch, implying greater densification.

The angle of repose, θ, has been used as a qualitative

measure for cohesiveness or the tendency of powdered or granulated materials to flow, for instance, from hoppers through the feed frame into tableting machines. Such uniformity of flow will minimize weight variations of the finished tablets (16). Angles of 30° or below usually indicate that the powder is free-flowing. An angle of 40° or above indicates poor flow. The angle of repose is affected by particle size distribution and usually increases with decreasing particle size. Both native starches exhibited poor flow. The flowability of a powder is a multifunctional parameter that depends on particle size and size distribution, shape, particle interactions, and moisture content (17). For powders with narrow size distributions, the flowability increases significantly with the increase in particle size. Powder shape determines the number of contact points between individual particles, which affects interparticle forces. Rough surfaces and irregular shapes can cause particles to interlock and resist bulk flow when shear stress is applied (17).

Swelling index

The swelling index shows the magnitude of the interaction between starch chains within the amorphous and crystalline domains. The extent of this interaction has been reported to be influenced by the amylose/amylopectin ratio and the characteristics of amylose and amylopectin in terms of molecular weight distribution, degree and length of branching, and conformation (18). Results of the swelling index are presented in Table 1 and these show that the Ofada rice starch showed significantly ($p<0.05$) greater swelling than corn starch. The difference in the swelling of the starches may be attributed to the difference in the intensity of molecular association forces inside the granules (19).

Compression behavior using the Kawakita model

Kawakita plots of P/C versus P are presented in Figure 3. The reciprocal of the values of the slope and intercept respectively yields the values of a and ab. Values of 1-a give the initial relative density of the starches, Di, while Pk values were obtained from the reciprocal values of b. The values of Di and Pk are

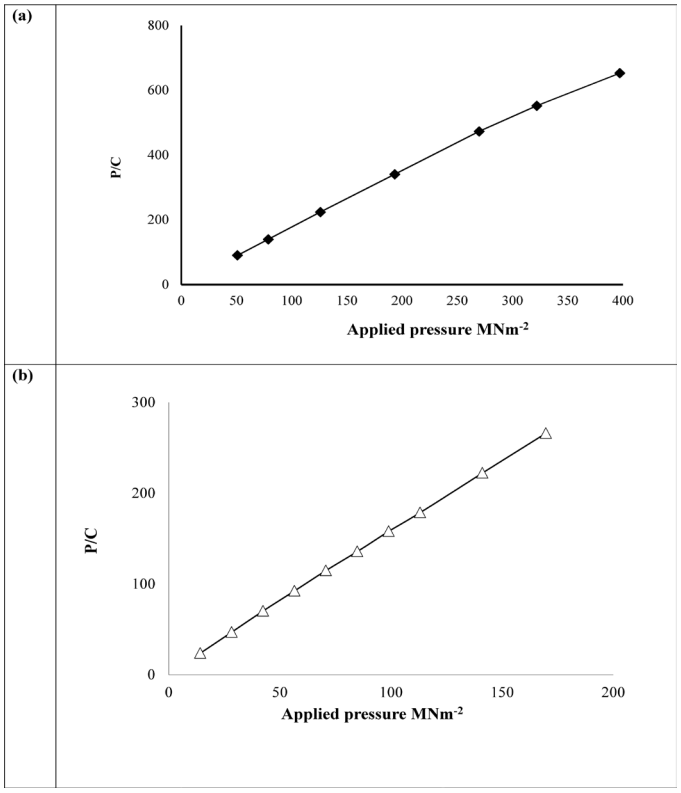

Figure 3 Kawakita plots for the tablets containing (a) Ofada starch and (b) Corn starch

presented in Table 1. The value of Di is a measure of the packed initial relative density of the formulation with the application of small pressure or tapping (20). The value of Pk is an inverse measure of the amount of plastic deformation occurring during the compression process. This value represents the pressure required to reduce the powder bed by 50% and is related to the deformability of the individual powder particles (21). Low values of Pk indicate materials that readily deform plastically under pressure. Ofada starch showed a faster onset of plastic deformation but corn starch gave a higher total amount of plastic deformation. However, it may be difficult to predict the deformation character of a multi-component system as plastic deformation is more complicated than for a single component (22).

Evaluation of chloroquine phosphate tablets

Tablet weight and thickness

The formulated chloroquine phosphate tablets passed weight variation as the percentage weight variation was

within the International Pharmacopeia limits of ±5% of the weight (23).

Mechanical and release properties

The results of the mechanical and release properties of the sixteen batches of chloroquine phosphate tablets are presented in Table 2. The results showed that crushing strength generally increased with the concentration of starch, compression pressure, and compression time. At similar compression pressures and compression times, the CP tablets containing Ofada rice starch had greater crushing strength at all concentrations tested. Testing for friability is important as the tablets are likely to be subjected to various abrasive motions during production and subsequent use. Friability decreased with an increase in binder concentration, compression pressure, and compression time for the tablets containing the Ofada starch. Conventionally compressed tablets that lose less than 1% of their weight during the friability test are generally considered acceptable (24). The friability tests showed that the formulations containing Ofada rice starch were less friable than those containing corn starch.

The disintegration of tablets determines to a large extent, the area of contact between the solid and liquid in the dissolution process (25). The CP tablet formulations containing Ofada rice starch had greater disintegration times at all concentrations, compression pressures, and compression times used. The disintegration time increased with an increase in the concentration of the starch binders, compression pressure, and compression time. The difference in the disintegration time with the concentration of starch binder emphasizes the need to optimize the level of starch binders used in tablet formulations to obtain tablets with the desired disintegration time.

It has been suggested that the crushing strength-friability-disintegration time ratio (CSFR/DT) provides a better index for measuring tablet quality because, in addition to measuring tablet strength (crushing) and weakness (friability), it simultaneously evaluates all negative effects of these parameters on disintegration

Table 2 Mechanical and release properties of sixteen batches of chloroquine phosphate tablets (mean ± and standard deviation, n=3)

BATCH	BINDER STARCH	BINDER CONCENTRATION % w/w	COMPRESSION PRESSURE MNm^{-2}	COMPRESSION TIME s	AVERAGE WEIGHT g	CRUSHING STRENGTH MNm^{-2}	FRIABILITY %	DISINTEGRATION TIME (Min)	CSFR/ DT	t_{80} (Min)
B_1	Corn	5.0	56.56	15.0	0.497±0.005	80.90±4.05	1.40±0.00	1.0±0.3	58.37	4.8±0.0
B_2	Corn	5.0	56.56	30.0	0.499±0.010	87.40±4.90	1.05±0.03	1.5±0.1	57.41	5.0±0.0
B_3	Corn	5.0	113.13	15.0	0.498±0.008	100.70±8.05	0.99±0.01	1.9±0.0	53.54	7.0±0.5
B_4	Corn	5.0	113.13	30.0	0.496±0.004	106.70±4.20	0.95±0.02	2.8±0.2	40.84	9.1±0.1
B_5	Corn	10.0	56.56	15.0	0.501±0.002	111.35±8.42	0.93±0.09	3.0±0.3	39.91	10.0±0.5
B_6	Corn	10.0	56.56	30.0	0.499±0.006	116.20±5.50	0.90±0.07	3.6±0.1	35.86	12.2±0.8
B_7	Corn	10.0	113.13	15.0	0.498±0.008	127.10±4.10	0.77±0.05	5.1±0.0	32.37	12.8±0.0
B_8	Corn	10.0	113.13	30.0	0.493±0.005	132.10±4.90	0.70±0.00	7.8±0.0	24.19	14.0±0.0
B_9	Ofada	5.0	56.56	15.0	0.497±0.005	85.60±3.85	0.90±0.03	0.8±0.1	118.89	3.8±0.3
B_{10}	Ofada	5.0	56.56	30.0	0.495±0.002	93.70±6.20	0.82±0.06	1.1±0.1	105.80	4.2±0.2
B_{12}	Ofada	5.0	113.13	15.0	0.495±0.006	101.24±8.00	0.98±0.07	1.2±0.2	86.09	5.1±0.0
B_{12}	Ofada	5.0	113.13	30.0	0.499±0.005	109.60±8.22	0.95±0.04	2.0±0.0	57.68	5.8±0.1
B_{13}	Ofada	10.0	56.56	15.0	0.495±0.003	97.50±7.05	0.90±0.05	2.4±0.0	46.10	7.0±0.0
B_{14}	Ofada	10.0	56.56	30.0	0.496±0.004	105.55±4.00	0.88±0.01	3.1±0.1	38.69	8.5±0.0
B_{15}	Ofada	10.0	113.13	15.0	0.496±0.010	124.70±7.56	0.75±0.02	4.5±0.0	36.95	9.1±0.1
B_{16}	Ofada	10.0	113.13	30.0	0.501±0.008	134.65±8.90	0.60±0.00	6.5±0.3	34.53	11.2±0.5

time (26). In general, greater values of the CSFR/DT ratio indicate a better balance between binding and disintegration properties.

The percentage of chloroquine phosphate released was plotted against time and plots for all batches of tablets (B_1 - B_{16}) are presented in Figures 4 (a) and (b). The values of t_{80} (i.e., the time required for 80% of the chloroquine phosphate to be released) were calculated from the plots. The formulations containing the Ofada rice starch reached greater t_{80} values compared to those containing the corn starches. Generally, dissolution time increased with binder concentration, compression pressure, and compression time.

The tablet formulations of chloroquine phosphate evaluated in this study were made without including a super disintegrant. In addition, the compression of the tablets was performed at a scale/speed that may not enable comparison to equivalent commercial product formulations

Experimental design

Tablets must have adequate mechanical strength to be able to withstand the rigors of handling and transportation experienced during process, in the drug distribution system, and in the field at the hands of the end-users (patients/consumers). Additionally, they must readily release the active pharmaceutical ingredient within a minimum time to ensure fast onset of drug action. Hence for the chloroquine phosphate tablet formulations, it is desired that the crushing strength-friability disintegration ratio should be maximized while the dissolution time for the tablet must be minimized.

In this study, the binder type and binder concentration were selected as formulation parameters while tablet compression pressure and compression time were selected as process parameters. The four input parameters were studied at two levels using the Taguchi method shown in Table 3. The experiments were carried out based on L-16 orthogonal array to give a total of 16 experimental runs and the data obtained for the two responses are presented in Table 4.

Table 3 Selected factors and their levels

FACTOR	SYMBOL	LEVEL	
		1 Low	2 High
Binder type	A	Ofada starch	Corn starch
Binder concentration (% w/w)	B	5.0	10.0
Compression pressure (MNm^{-2})	C	56.56	113.13
Compression time (s)	D	15.0	30.0

Taguchi analysis was used to evaluate the main effects of individual parameters by calculating the S/N ratio plots for CSFR/DT and t_{80}, using the greater-the-better and the lower-the better parameters, respectively. The main effect plots and interaction plots obtained are shown in Figures 5 and 6 respectively. From these plots, optimum factor levels for both CSFR/DT and t_{80} was A2, B1, C1, D1. This refers to Batch 9 in which the CP formulations contain Ofada rice starch at 5% w/w and were compressed using 56.56 MNm^{-2} for a period of 15 seconds, presented in Table 5.

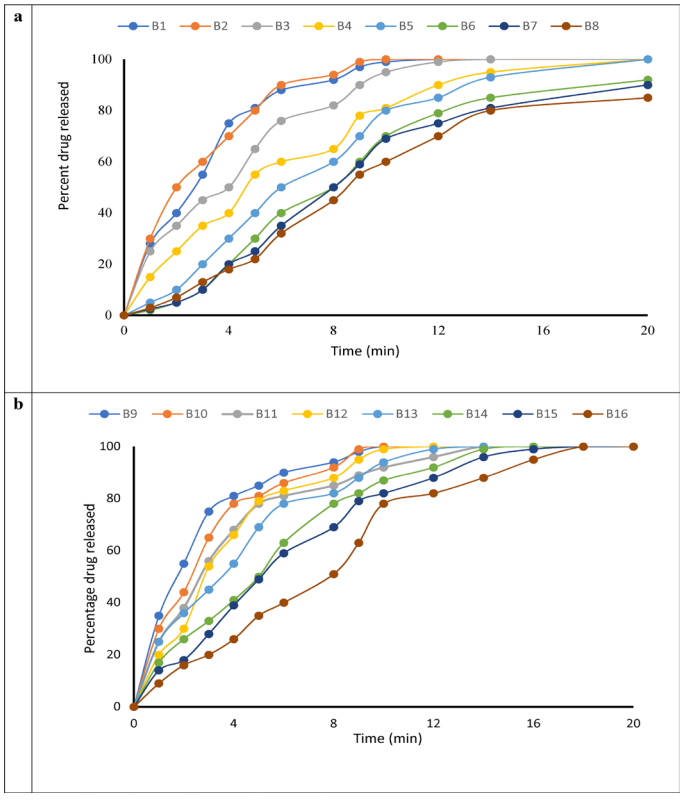

Figure 4 Plot of percent Chloroquine phosphate released vs time for (a) batches B_1-B_8 and (b) batches B_9 –B_{16}

Table 4 Taguchi's L16 standard orthogonal array

BATCH	A B C D	BINDER TYPE	BINDER CONCENTRATION % w/w	COMPRESSION PRESSURE MNm^{-2}	COMPRESSION TIME (s)	CSFR/DT	t_{80} (Min)
B_1	1 1 1 1	Corn	5.0	56.56	15.0	58.37	4.80
B_2	1 1 1 2	Corn	5.0	56.56	30.0	57.41	5.00
B_3	1 1 2 1	Corn	5.0	113.13	15.0	53.54	7.00
B_4	1 1 2 2	Corn	5.0	113.13	30.0	40.84	9.10
B_5	1 2 1 1	Corn	10.0	56.56	15.0	39.91	10.00
B_6	1 2 1 2	Corn	10.0	56.56	30.0	35.86	12.20
B_7	1 2 2 1	Corn	10.0	113.13	15.0	32.37	12.80
B_8	1 2 2 2	Corn	10.0	113.13	30.0	24.19	14.00
B_9	2 1 1 1	Ofada	5.0	56.56	15.0	118.89	3.80
B_{10}	2 1 1 2	Ofada	5.0	56.56	30.0	105.80	4.20
B_{11}	2 1 2 1	Ofada	5.0	113.13	15.0	86.09	5.10
B_{12}	2 1 2 2	Ofada	5.0	113.13	30.0	57.68	5.80
B_{13}	2 2 1 1	Ofada	10.0	56.56	15.0	46.10	7.00
B_{14}	2 2 1 2	Ofada	10.0	56.56	30.0	38.69	8.50
B_{15}	2 2 2 1	Ofada	10.0	113.13	15.0	36.95	9.10
B_{16}	2 2 2 2	Ofada	10.0	113.13	30.0	34.53	11.20

Analysis of variance (ANOVA) was used to determine the relative influence of each factor and the results are presented in Table 6. ANOVA analysis revealed that binder concentration was the most significant parameter that influenced both CSFR/DT and t_{80} with $p = 0.000$, establishing the significance of the factor.

The effect of the concentration of disintegrant could be due to the fact that the greater the amount of starch as disintegrant exposed to the disintegrating fluid, the greater the amount of water absorbed and subsequent generation of greater swelling force to facilitate disintegration (27). On the other hand, the interaction between A and B (binder type and binder concentration) had the greatest effect on CSFR/DT and t_{80}, even though the effect was not significant ($p > 0.05$).

Table 5 Optimum factor levels for CSFR/DT and t_{80}

FACTOR	SYMBOL	LEVEL	VALUE	UNIT
Binder type	A	2	Ofada	
Binder concentration	B	1	5.00	% w/w
Compression pressure	C	1	56.56	MNm^{-2}
Compression time	D	1	15.00	s

To determine the level of the various factors that will simultaneously maximize the responses, the values of CSFR/DT and t_{80} were normalized and the

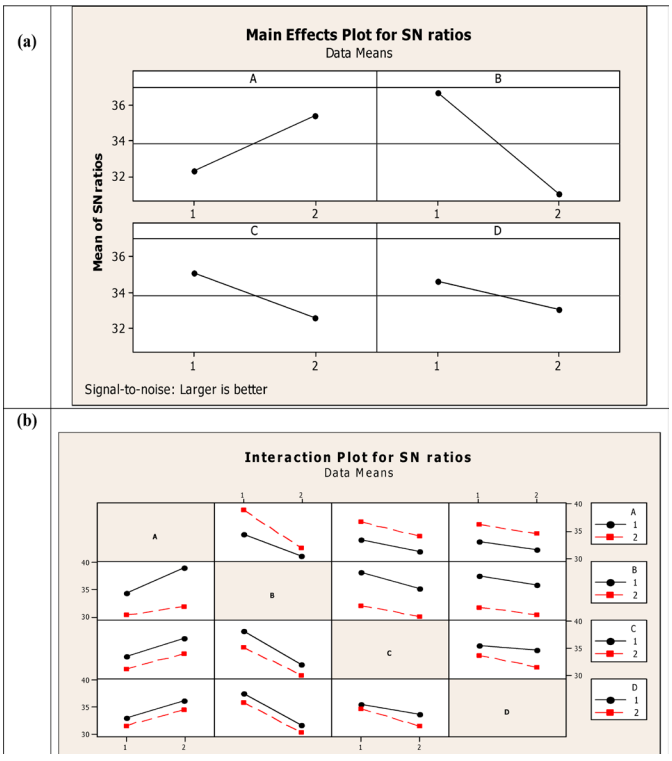

Figure 5 (a) Main effect plots and (b) interaction plots of S/N ratio for CSFR/DT

Table 6 Analysis of variance (ANOVA) for CSFR/DT and t_{80}

RESPONSE	SOURCE	DF	SEQ SS	ADJ SS	ADJ MS	F	P
CSFR/DT	A	1	38.335	38.335	38.335	36.07	0.002
	B	1	127.009	127.009	127.009	119.51	0.000
	C	1	24.824	24.824	24.824	23.36	0.005
	D	1	9.856	9.856	9.856	9.27	0.029
	A*B	1	9.704	9.704	9.704	9.704	0.029
	A*C	1	0.259	0.259	0.259	0.24	0.642
	A*D	1	0.026	0.026	0.026	0.02	0.882
	B*C	1	0.825	0.825	0.825	0.78	0.419
	B*D	1	0.126	0.126	0.126	0.12	0.745
	C*D	1	1.782	1.782	1.782	1.68	0.252
	Residual Error	5	5.314	5.314	1.063		
	Total	15	218.060				
			R-Sq = 98.8% R-Sq (adj) = 96.3%				
t_{80}	A	1	25.503	24.503	25.503	63.92	0.000
	B	1	100.000	100.000	100.000	250.63	0.000
	C	1	21.623	21.623	21.623	54.19	0.001
	D	1	6.760	6.760	6.760	16.94	0.009
	A*B	1	2.402	2.402	2.402	6.02	0.058
	A*C	1	0.640	0.640	0.640	1.60	0.261
	A*D	1	0.062	0.062	0.062	0.16	0.709
	B*C	1	0.003	0.003	0.003	0.01	0.940
	B*D	1	0.810	0.810	0.810	2.03	0.214
	C*D	1	0.202	0.202	0.202	0.51	0.508
	Residual Error	5	1.995	1.995	0.399		
	Total	15	160.000				
			R-Sq = 97.6% R-Sq (adj) = 92.7%				

normalized data table was then used to calculate the deviation sequence followed by the determination of the Grey relational coefficient values. From the mean values of the Grey relational coefficient for both responses, the Grey relational grade was obtained, thus converting this multi-objective optimization into a single optimization. The results of the normalized data, deviation sequence, Grey relational coefficients, Grey relational grade, and rank are presented in Table 7. The overall performance characteristics of the multiple response processes depend on the calculated Grey relational grade. A greater grey relational grade implies that the corresponding parameter combination is closer to the optimal set of input parameters (28). The ranking show that the best formulation was Batch B9 containing the Ofada starch as a binder at a concentration of 5% w/w, compressed at 56.56 MNm^{-2} for a period of 15 seconds. A Taguchi analysis was used to calculate the S/N ratio plot for the Grey relational grade using the higher-the-better since S/N ratio is always maximized irrespective of the quality characteristics of the responses.

The results showed the delta values and rank and are presented in Table 8. The ranking of the parameters showsshow that binder concentration is the most effective parameter. The main effect of the plots and the interaction plots are shown in Figures 6a and 6b, respectively. The plots show that the optimum parametric combination of the factors were A2, B1, C1, D1.

The optimum parameter levels for CSFR/DT and t_{80} based on the main effect plots, illustrated in Figures 4 and 5, respectively, were A2, B1, C1, D1 similar to the optimal level based on the Taguchi based grey-relational design shown in Figure 6. The confirmation test at the optimal parameter setting was then conducted to evaluate the quality characteristics for the formulation of chloroquine phosphate tablets. Thus

Table 7 Results of Grey Taguchi calculations

BATCH	GREY RELATIONAL GENERATION		DEVIATION SEQUENCE		GREY RELATIONAL COEFFICIENT		GREY RELATIONAL GRADE	
	CSFR/DT	t_{80}	CSFR/DT	t_{80}	CSFR/DT	t_{80}	GRG	RANKING
B_1	-0.639	0.902	0.639	0.098	1.317	0.836	1.076	4
B_2	-0.649	0.882	0.649	0.118	1.305	0.810	1.057	5
B_3	-0.690	0.686	0.690	0.314	1.260	0.614	0.937	7
B_4	-0.824	0.480	0.824	0.520	1.133	0.490	0.812	10
B_5	-0.834	0.392	0.834	0.608	1.124	0.451	0.788	12
B_6	-0.877	0.176	0.877	0.824	1.090	0.378	0.734	14
B_7	-0.914	0.118	0.914	0.882	1.061	0.362	0.711	15
B_8	-1.000	0.000	1.000	1.000	1.000	0.333	0.667	16
B_9	0.000	1.000	0.000	0.000	3.000	1.000	2.000	1
B_{10}	-0.138	0.961	0.138	0.039	2.350	0.927	1.639	2
B_{11}	-0.346	0.873	0.346	0.127	1.772	0.797	1.285	3
B_{12}	-0.646	0.804	0.646	0.196	1.308	0.718	1.013	6
B_{13}	-0.769	0.686	0.769	0.314	1.182	0.614	0.898	8
B_{14}	-0.847	0.539	0.847	0.461	1.114	0.520	0.817	9
B_{15}	-0.865	0.480	0.865	0.520	1.099	0.490	0.795	11
B_{16}	-0.891	0.275	0.891	0.725	1.079	0.408	0.743	13

formulation of chloroquine phosphate tablets was prepared using Ofada rice starch at a concentration of 5 % w/w at a compression pressure of 56.56 MNm^{-2} and compression time of 15 seconds. The response values obtained from the confirmation experiment (CSFR/DT = 120.55 and t_{80} = 4.00 min) was found to be similar that of the initial experimental run (CSFR/DT = 118.89 and t_{80} = 3.80 min).

The DoE results were applied to the methodology of tableting performed and may require further studies to be extrapolatable to commercial tableting conditions.

Table 8 Response table of Signal-to-Noise Ratios for GRG

LEVEL	A	B	C	D
1	-1.56150	1.41826	0.49804	0.03881
2	0.66744	-2.31232	-1.39210	-0.93287
Delta	2.22894	3.73058	1.89014	0.97168
Rank	2	1	3	4

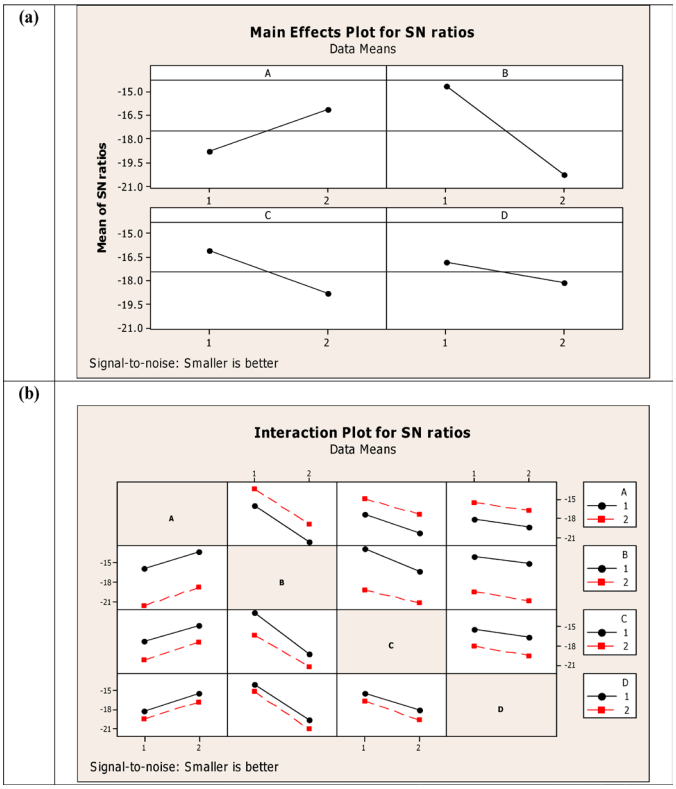

Figure 6 (a) Main effect plots and (b) interaction plots of S/N ratio for t_{80}

CONCLUSIONS

The morphology and material properties of the Ofada rice starch varied in comparison to the widely used corn starch. A Taguchi based grey-relational design showed that binder concentration was the most significant parameter that affected both CSFR/DT and t_{80} in the chloroquine phosphate tablets while the interaction between binder type and binder concentration had the greatest influence on both responses. The optimized formulation contained Ofada rice starch at a concentration of 5% w/w compressed at 56.546 MNm^{-2} at a compression time of 15 seconds. Thus, native Ofada starch could be a useful binder in tablet formulations that require a good balance between mechanical strength and fast release of a drug.

REFERENCES

1 Rogerson SJ. Management of malaria in pregnancy. Indian J. Med. Res. 146(3): 328 – 333, 2017.

2 Payne D. Spread of chloroquine resistance in Plasmodium falciparum. Parasitol Today 3(8):241–246, 1987.

3 Danbaba N, Anounye JC, Gana AS, Abo ME, Ukwungwu MN, Grain quality characteristics of Ofada rice (Oryza sativa L.): Cooking and eating quality, Int. Food Res. J 18: 629-634, 2011.

4 Equbala MI, Randhir K, Shamimc M, Ohdard RK. A grey-based Taguchi method to optimize hot forging process. Procedia Mat. Sci 6: 1495 – 1504, 2014.

5 Jangraa, K., Grovera, S. and Aggarwal, A.. Simultaneous optimization of material removal rate and surface roughness for WEDM of WCCo composite using grey relational analysis along with Taguchi method. Int. J. Ind. Eng Comput 2: 479-490, 2011

6 Singh H and Kumar P. Optimizing cutting force for turned parts by Taguchi's parameter design approach. The Ind. J. Eng and Mat. Sci 12(2):97–103, 2005.

7 Kumar S, Chary GHVC, Dastidar MG. Optimization studies on coal–oil agglomeration using Taguchi (L16) experimental design. Fuel. 141:9 16, 2015.

8 Okunlola A. Flow, compaction and tabletting properties of co-processed excipients using pregelatinized Ofada rice starch and HPMC. J. Excip. Food Chem 9(1): 4 – 15, 2018.

9 Bowen FE and Vadino WA. A simple method for differentiating sources. Drug Dev. Ind. Pharm. 10: 505-511, 1984.

10 Kawakita, K and Ludde, K.H. Some considerations on powder compression equations Powder Technology 4:61-68, 1970/71.

11 Fell, J.T. and Newton, J.M. Determination of tablet strength by diametral compression test. Journal of Pharmaceutical Sciences 59:688-691, 1970.

12 Ross TJ. Taguchi techniques for quality engineering. McGraw-Hill Book Company, New York, 1988.

13 Wray, P.E. The physics of tablet compression revisited Drug Dev. Ind. Pharm. 18: 627-658, 1992.

14 Odeku, O.A and Picker-Freyer, K.M. Analysis of the material and tablet formation properties of four Dioscorea starches. Starch/Stärke 59: 430-444, 2007.

15 Carr, R.L. Evaluating flow properties of solids. Chem Eng J. 72: 163-168, 1965.

16 Varthalis, S. and Pilpel, N. Anomalies in some properties of powder mixtures. J Pharm and Pharmacol 28: 415 – 419, 1976.

17 Ganesan V, Rosentrater KA, Muthukumarappan K. Flowability and handling characteristics of bulk solids and powders - a review with implication for DDGS. Biosyst Eng 101: 425-435, 2008.

18 Hoover, R. Composition, molecular structure and physicochemical properties of tuber and root starches: a review. Carbohydr. Polym 4: 253-267, 2001.

19 Zhang Z, Tian X, Wang P, Jiang H and Li W. Compositional, morphological and physicochemical properties of starches from red Adzuki bean, Chicken pea, Faba bean and Baiyue bean grown in China. Food Sci &Nutri 7: 2485 – 2494, 2019.

20 Odeku O.A. and Itiola O.A. Evaluation of Khaya gum as binding agent in tablet formulation. Pharm and Pharmacol Comm 4: 183-188, 1998.

21 Lin, C. and Cham, T. Compression behavior and tensile strength of heat treated polyethyleneglycols. Int. J. Pharm 118:169-179, 1995.

22 Ilić I, Janković B, Šibanc R, Srcic S, Dreu R. Deformation properties of pharmaceutical excipients determined using an in-die and out-die method Int. J. Pharm Int. J. Pharm 446(1-2):6-15, 2013

23 World Health Organization. (WHO) . The International pharmacopoeia (Pharmacopoea internationalis), 3rd ed. World Health Organization, 2003. https://apps.who.int/iris/handle/10665/38009.

24 British Pharmacopoeia. The Pharmaceutical Press, Her Majesty's Stationery Office, London. I: 379, 969, 1242, 1998.

25 Itiola, O.A. and Pilpel, N. Formulations effects on the mechanical properties of metronidazole tablets. J. Pharm. Pharmacol 43: 145-147, 1991.

26 Luangtanan-Anan, M. & Fell, J.T. Bonding mechanisms in tableting. International Journal of Pharmaceutics. 60: 197-202, 1990.

27 Wan, L.S.C. and Prasad, K.P.P. Uptake of water into tablets with low substitute carboxymethyl cellulose sodium as

disintegrant. Int. J. Pharm. 55:115-121, 1989.

28 Gul, M, Shah AN, Aziz U, Husnain N, Mujtaba MA, Kousar T, Ahmad R and Hanif MF (2019): Grey-Taguchi and ANN based optimization of a better performing low-emission diesel engine fueled with biodiesel, Energy Sources, Part A: Recovery, Utilization, and Environmental Effects, DOI: 10.1080/15567036.2019.1638995.