A QUALITY BY DESIGN (QBD) APPROACH OF ASSESSING THE EFFECT OF SUPER DISINTEGRANT PROPERTY OF *KHAYA SENEGALENSIS* GUM ALONE AND IN COMBINATION WITH STANDARD SUPER DISINTEGRANTS IN METRONIDAZOLE TABLET PREPARED BY DIRECT COMPRESSION

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ABSTRACT

Purpose: The aim of this study is to use quality by design approach to assess the effect of a natural polymer, *Khaya senegalensis* gum (KSG) alone and in combination with Crospovidone (CPV) and Sodium starch Glycolate (SSG) as super disintegrants in metronidazole tablets formulated via direct compression.

Principal methodology: Design of Experiments (DoE) was employed to derive the formulation matrix for the three components KSG, SSG & CPV as well as the ratio for the optimized formulation, coded equations and contour lines of observed effects on the responses including disintegration time (DT), Crushing strength (CS) & Friability (FR). The powders were mixed in the ratio generated and directly compressed using a pair of 12 mm punches on a single punch tableting machine at a compression pressure of 8 MT to produce 650 mg unit of tablets.

Key findings: The resulting effect of the responses revealed that, KSG and SSG both conferred strength to the tablets and produced the least friable tablets at high, moderate and low levels. On the other hand, tablets containing CPV produced the softest and most friable tablets. However, DT was rapid for all runs ranging between 7.5 to 11.6 seconds with KSG runs taking the longest time. The optimized formulation contained KSG (2.856%) & SSG (5.144%) only as given by the desirability function.

Conclusion: The effect of the mixture components was an effective reduction in DT, FR and acceptable CS only where KSG levels were present from 1.33 to 8%w/w while the optimized formulation was seen to be valid for its close similarities with the predicted values. This shows that *Khaya senegalensis* gum can be used as a super disintegrant in conventional metronidazole tablets manufactured by direct compression most especially where fast disintegration and tablet robustness is required.

Keywords: direct compression, immediate release, *Khaya senegalensis*, metronidazole, optimized, super disintegrant
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INTRODUCTION

Disintegrating agents are added to tablet formulations to aid break-up of the compacted mass into the primary particles once in contact with aqueous milieu to facilitate the dissolution or release of the active ingredients. Substances that break up tablets instantly or more rapidly than the conventional tablet disintegrants have been developed. These substances called super disintegrants are added to tablet formulations in low concentrations, typically 1 - 10% by weight to facilitate tablet break up within a few seconds to minutes [1, 2]. Super disintegrants are available as synthetic or semi synthetic polymers e.g. Crospovidone, Croscarmellose sodium and Sodium starch glycolate have been in common use and recently natural polymers have been discovered as super disintegrants. Mentions have been made of plant gums and mucilages like mango peel pectin, Ispaghula husk, Guar, Karaya and locust bean gums for exhibiting super disintegrant property [3].

Khaya senegalensis gum (KSG) that exudes from the bark of *Khaya senegalensis* tree either by incision or due to unfavourable conditions of heat or drought is the gum of interest in this research. The gum dispersion was reported to be mildly acidic and slightly soluble in water with a high viscosity. In addition, it absorbs water readily and swells to about 10 times its original weight [4]. According to the author, these properties rendered its use as a suspending agent, tablet binder, disintegrant as well as a matrix former [5–7]. Odeku *et al*. [8] advocated the development of Khaya gum as a commercial binding agent for particular tablets. It was described to provide similar tablet binding action as acacia [9] with a preferred mechanical strength over another of its species, *grandifolia* [8]. In a recent research, a two-mixture component of natural excipients, KSG and Sammaz maize starch (SMS) used as disintegrants displayed super disintegrant property in metronidazole tablets compressed via direct compression. The combination yielded non-friable metronidazole tablets with adequate crushing strength and very low disintegration time of ≤ 1 minute [10].

To explore further the super disintegrant action of KSG, a more systematic approach where interactions of two or more variables acting differently together compared to their separate effect was employed, this time using standard super disintegrants. The aim of this study is thus, to use quality by design approach to assess

the effect of *Khaya senegalensis* gum (KSG) alone and in combination with Crospovidone (CPV) and Sodium Starch Glycolate (SSG) as super disintegrants as well as to select an optimized concentration of this combination as super disintegrants in metronidazole tablets formulated via direct compression. So far, the super disintegrant property of KSG has not been determined using this approach.

MATERIALS AND METHODS

Materials

Metronidazole powder (Central Drug House® New Delhi -110002, India), *Khaya senegalensis* gum powder (≤ 250µm) extracted from the crude gum via aqueous dispersion and precipitation by organic solvent. Microcrystalline cellulose, Crospovidone and Sodium Starch Glycolate were obtained as a gift from JRS Pharma, Germany, Magnesium Stearate and Talc (BDH Chemicals, England). All other ingredients were of analytical grade.

Experimental design

A mixture design was generated using Design Expert Software ver.10 for the formulation of a three (3) mixture components, *Khaya senegalensis* gum (KSG), Sodium Starch Glycolate (SSG) & Crospovidone (CPV) with three responses, disintegration time (DT), crushing strength (CS) and friability (FR) for metronidazole tablets. The concentrations of the components varied from 0 – 8 % each and a total of fourteen experimental levels/runs were developed. For each run, other ingredients in quantities listed in Table 1 were added and tumbled mixed for 2 min then directly compressed on a single punch tableting machine (Erweka, AR 400, Germany) using 12 mm punches at a compression pressure of 8 metric tons to produce 650 mg unit of tablets. The formulated tablets were each tested for DT, CS and FR. The experimental levels and the resulting responses are shown in Table 2. These responses were fitted to a selected model based on the design and statistically analyzed. The optimized formulation was determined and the coded equations and other tablet tests were used to describe the behavior of the mixture components.

Table 1: Formula for metronidazole tablets containing various disintegrants

Ingredient	Quantities (%w/w)
Metronidazole powder	30.77
Microcrystalline Cellulose	60.63
Magnesium stearate	0.5
Talc	0.1
Disintegrant (as given in Table 2)	q.s.

Tablet evaluation

Weight variation test, thickness and diameter test: Twenty (20) tablets were selected from each batch and weighed individually on an electronic balance (CAS-304- Gallenkamp, England). The average weight was recorded and the relative standard deviation was calculated. A Vernier caliper was used to measure the thickness and diameter of each of the 20 tablets. The average thickness and diameter as well as the relative standard deviations were calculated.

Friability test: Ten (10) tablets from each batch were dedusted and weighed after which they were transferred into a Roche friabilator (type TA3R, Germany) which was set to run at 25 rpm for 4 min. The tablets were then collected, dedusted and reweighed. From the result, friability was calculated as % weight loss.

Crushing strength: A Monsanto hardness tester (MHT 35-Cambell Electronics, U.S.A) was used to crush diametrically 10 tablets taken at random from each run. The force (KgF) required to break each of the tablets was recorded and the average value was calculated.

Disintegration test: Six (6) tablets of equal weight were selected from each run and placed in the tubes of a disintegration tester (ZT3 Erweka, Germany) containing the disintegration fluid (0.1 N HCl) maintained at a temperature of 37 ± 0.5°C to mimic *in vivo* conditions. The time taken for the individual tablets to disintegrate completely without any palpable mass was recorded. The mean disintegration time for each batch was calculated.

Dissolution: *In vitro* drug release studies were performed using USP apparatus 1 (basket method). The dissolution medium was 900 ml of 0.1 N HCl maintained at 37 ± 0.5°C to simulate the gastric medium where the tablets will disintegrate and subsequently dissolve. In all experiments, 5 ml aliquots were withdrawn at time points of 0, 5, 30, 60 seconds with replacement of 5 ml fresh dissolution medium (at same temperature) after each withdrawal to maintain sink condition. The samples were assayed spectrophotometrically (model UV-1800 Shimadzu, USA) at 277nm for metronidazole.

Content uniformity: To determine the amount of drug present in each tablet, 3 tablets were randomly selected from each batch and then crushed. The equivalent of one tablet (650mg) was weighed out and dissolved in

100 ml of 0.1N HCl, the solution was shaken vigorously and then filtered. A 10-fold dilution of the samples was then made, filtered and assayed spectophotometrically at 277 nm for metronidazole. The drug content was calculated in percentage (%).

RESULTS AND DISCUSSION

Table 2: Experimental levels of KSG, SSG & CPV for each formulation and the resulting responses obtained

Run	Component 1: A KSG%	Component 2: B SSG%	Component 3: C CPV %	Response 1: DT (sec)	Response 2: CS (KgF)	Response 3: FR (%)
1	4.00	4.00	0.00	8.2	6.9	0.15
2	0.00	8.00	0.00	11.3	6.1	0.46
3	2.67	2.67	2.67	7.6	4.5	0.92
4	5.33	1.33	1.33	6.8	6.4	0.46
5	4.00	0.00	4.00	7.8	5.7	0.47
6	0.00	0.00	8.00	6.8	3.7	2.94
7	8.00	0.00	0.00	11.6	6.6	0.3
8	1.33	5.33	1.33	8.5	6.3	0.48
9	0.00	8.00	0.00	8.3	5.9	0.46
10	1.33	1.33	5.33	7.9	5.3	0.62
11	0.00	0.00	8.00	7.5	2	27.24
12	8.00	0.00	0.00	8.3	6.2	0.46
13	0.00	4.00	4.00	8	1.8	6.61
14	4.00	4.00	0.00	7.7	4.6	1.07

Table 3: Analysis of Variance of the three Response Variables Using the Experimental Design

Responses	source	Sum of squares	df	Mean square	F value	p-value prob>F	R squared	Adjusted. R^2	Adeq. precision
DT	Model	13.99	5	2.80	1.80	0.2190	0.5295	0.2354	3.179
	[1]Linear Mixture	6.80	2	3.40	2.19	0.1747			
	AB	6.11	1	6.11	3.93	0.0828			
	AC	0.91	1	0.91	0.58	0.4669			
	BC	0.094	1	0.094	0.060	0.8122			
	Residual	12.44	8	1.55					
	Lack of Fit	2.12	4	0.53	0.21	0.9227			
	Pure Error	10.31	4	2.58					
	Cor Total	26.43	13						
CS	Model	19.83	2	9.92	7.23	0.0099	0.5681	0.4895	6.960
	[1]Linear Mixture	19.83	2	9.92	7.23	0.0099			
	Residual	15.08	11	1.37					

	Lack of Fit	10.89	7	1.56	1.49	0.3687			
	Pure Error	4.19	4	1.05					
	Cor Total	34.91	13						
FR	Model	260.82	2	130.41	3.52	0.0658	0.3903	0.2794	4.522
	[1]Linear Mixture	260.82	2	130.41	3.52	0.0658			
	Residual	407.45	11	37.04					
	Lack of Fit	111.77	7	15.97	0.22	0.9617			
	Pure Error	295.68	4	73.92					
	Cor Total	668.27	13						

Effect of changing levels of component excipients (Factors) on response DT, CS and FR

Disintegration is a pre-requisite to bioavailability as well as elicitation of pharmacologic effect of an active drug in a solid dosage form. A disintegrant is usually added to a tablet formulation to achieve rapid disintegration into aggregates and subsequently into primary particles that dissolve to release the drug for absorption. Disintegration time was between 6.8 to 11.6 seconds for the runs (table 2). The DT, CS values of component KSG were only slightly higher than those of SSG and the FR was also similar. The two components when employed at maximum disintegrant concentration (8% w/w) alone, behaved similarly with respect to the three responses. They produced tablets with good mechanical strength and friability values of less than 1.0 %. Contrarily CPV employed alone as disintegrant at maximum concentration was faster to disintegrate than both KSG and SSG and also produced the most friable and softest tablets.

A two-component mixture of KSG with SSG was only slightly higher in DT & CS than KSG with CPV. Friability in both cases was lower than 1% but better with KSG and SSG mixture. Mixtures of components SSG & CPV only produced soft and very friable tablets but with similar DT as the above two combinations. The combination of the three components in same proportion (Run 3, Table 2) yielded tablets with rapid DT, acceptable hardness and friability. When KSG was higher in the three combination, DT was shortest, CS was highest and FR was lowest compared to SSG and CPV employed at highest concentration (Runs 8 &10 respectively). The ability of KSG to confer strength on the tablets and at the same time decrease DT was thus evident (Run 4). Moreover, effective super disintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs [3, 11]. The values of DT varied across the formulations because of the changing proportions of the factors. Summary statistics of the model fitted to response DT is given in Table 4. The R^2 = 0.2354, F value 1.80 and adequate precision of 3.18 indicated that the model was not adequate to navigate the design space. Analysis of variance confirmed that the model is not significant at $p < 0.05$. This means that the varied factors had no effect on the response DT, thus imparted the response in a similar manner. The regression equation generated for DT in terms of actual components is given as

$$DT = +1.22077 * KSG + 1.23208 * SSG + 0.90777 * CPV - 0.12677 * KSG * SSG - 0.058557 * KSG * CPV - 0.018825 * SSG * CPV$$

The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients. A positive coefficient represents a synergistic effect, whereas a negative coefficient indicates an opposite effect on the response; moreover, a greater coefficient indicates that the independent variable has a stronger effect on the response[12, 13]. All three factors individually had a positive effect on DT, Factor A (KSG) & Factor (B) SSG being higher than factor C (CPV). Interaction terms with negative (-) signs were more favourable for reduction of DT. These negative effects were more pronounced with BC >AC >AB. Factors B & C are standard super disintegrants used to speed drug disintegration and as such expected to disintegrate faster.

Crushing strength and friability are the measure of strength or weakness of a tablet respectively. Friability test is used to evaluate the tablet's resistance to abrasion while crushing strength assesses the ability of the tablet to withstand handling without fracturing or chipping. Hardness (crushing strength) can also influence friability and disintegration in some cases. The harder the tablet the less friable and more time it takes to disintegrate [14]. The results of response CS for the 14 runs of experiment are presented in Table 2 with

values ranging from 1.8 to 6.9 KgF. Runs 6, 11 & 13 failed the test falling out of the acceptable hardness limits of 4 - 8 KgF given by manufacturers. Changes in factor levels as well as factor type were seen to affect tablet hardness. Higher CS values were obtained where levels of KSG were either high or moderate in proportion and least values were obtained where the component was CPV. The component CPV had the least effect on response CS. The response CS was described by a linear mixture model (Table 3). The model was statistically significant at $p<0.05$, with a non-significant lack of fit indicating that the model fitted well. The predicted R^2 of 0.3656 was in reasonable agreement with the adjusted R^2 0.4895 with a high adequate precision 6.960, an indication that the model can be used to navigate the design space. The equation below described the response.

$$CS = +6.69722 * KSG + 5.57722 * SSG + 2.92466 * CPV$$

For identifying the relative impact of the factors by comparing the factor coefficients, the coded equation finds importance. Factor A (KSG)>B(SSG) > C(CPV). The coefficient of terms further explained that increase in CS was favoured by increasing levels of KSG. The positive signs of the coefficient of components (Factors) revealed the extent each component affected response CS.

The linear mixture model was used to generate the statistics of response FR (friability) on the varying factor levels. An F-value of 3.52 at $p<0.05$ indicated that the model is not significant relative to the noise. The lack of fit was also not significant and implied that the linear mixture model fits. Adequate precision of 4.522 indicates an adequate signal and the model can be used to navigate the design space.

$$FR = -1.34464 * KSG - 0.048637 * SSG + 11.3940 * CPV$$

The coded equation above revealed that components KSG and SSG decreased friability while CPV drastically increased friability. This was also depicted in Table 2 Runs 6, 11 and 13 with high % friability values which caused a decrease in tablet strength and resulted to soft tablets. According to USP (2010), for a tablet to withstand abrasion during packaging, handling and shipping or transportation, it should have a friability of ≤ 1.0 %. The contour lines showing effect of components on responses are depicted in Figures 1 a, 1b and 1c.

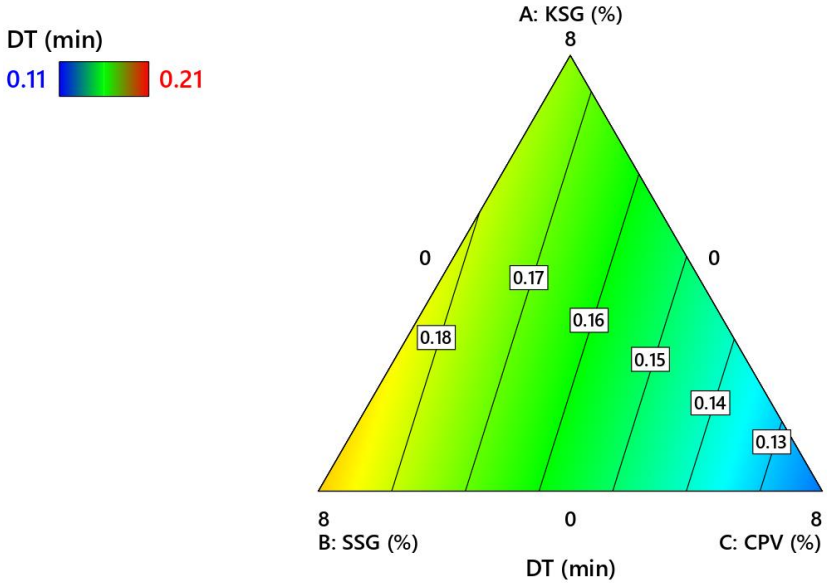

Figure 1a: Contour plot showing effect of the individual components of the formulation matrix on the disintegration time (DT) of the tablets formulated by direct compression.

The contour plot shows that increasing the content of KSG from 0 to 8 % increased the DT of tablets this is akin to SSG as increasing the concentration of SSG from 0 to 8 % led to an increase in DT. However, there was a decrease in DT when the content of CPV was increased from 0 to 8 %.

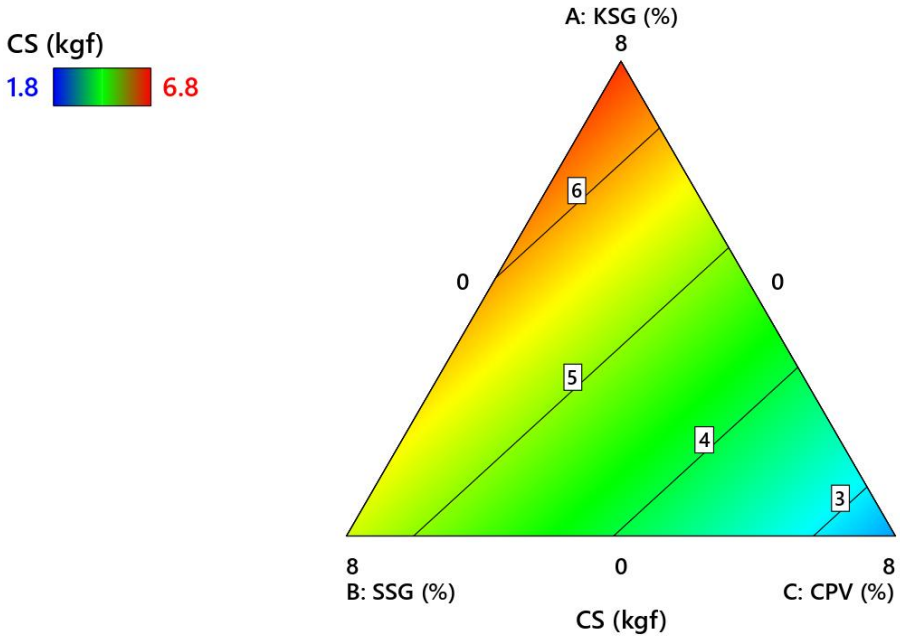

Figure 1b: Effect of the individual components of the formulation matrix on the CS of tablets developed by direct compression.

Increasing the concentration of KSG across the formulations from 0 to 8 % increased the CS of tablets while the reverse was the case when the content of CPV was increased from 0 to 8 %. Increasing the concentration of SSG from 0 to 8 % did not appear to have a significant effect on CS of tablets.

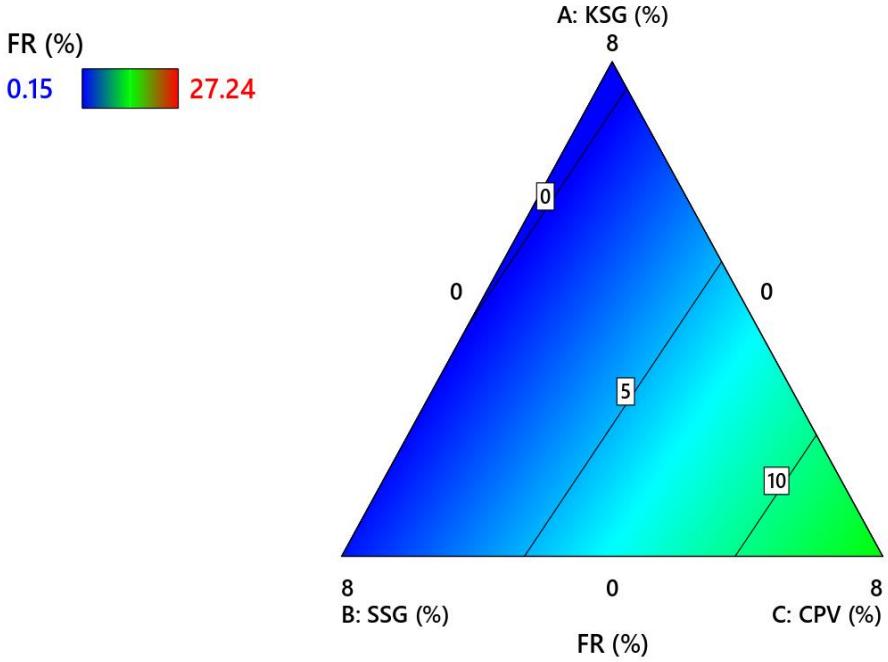

Figure 1c: Contour plots showing effect of the individual components of the formulation matrix on the FR of tablets generated by direct compression.

There was a decrease in FR values when the content of KSG was increased from 0 to 8 % this was similar to SSG while the values of FR increased when the content of CPV increased from 0 to 8 %.

Optimization studies

A similar criteria as described by Mahmud *et al.* and Apeji *et al.* [10, 15] using the numerical optimization method to determine the factors and responses for the optimized formulation was adopted. A single solution with a desirability function of 0.769 was obtained as the possible combination to predict an optimized metronidazole tablet formulation containing only two of the three components (factors) as disintegrants. The desirability value tended towards 1.0, which is an indication that all parameters set for the criteria were nearly achieved. Table 4 shows the quantities of disintegrants as well as the evaluated response variables of the optimized formulation. Although DT and FR values widely varied from the prediction, they remained within acceptable range for these parameters in terms of tablet quality and hence the model can be considered valid. The overall quality of formulated tablets was further described using the general formulation properties (Table 5).

Table 4: Prediction and outcome of factors and responses of optimized metronidazole tablet formulation containing KSG and SSG as super disintegrants

Optimized formulation	KSG (%w/w)	SSG (%w/w)	DT (sec)	CS (KgF)	FR (%)	Desirability
prediction	2.856	5.144	11.04	5.77	0.152	0.769
Outcome	2.856	5.144	29.30	6.00	0.617	-

DT=disintegration time, CS= crushing strength, FR= friability

Table 5: Average values of parameters assessed for metronidazole tablets formulated using KSG, SSG & CPV either alone or in combination as super disintegrants

Parameter	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8	Run 9	Run 10	Run 11	Run 12	Run 13	Run 14	Optimized
Weight (mg)	652 ± 13.6	644.5 ±11.2	640 ± 11.4	652 ±12.8	637.5± 11.8	634 ± 10.68	649 ± 9.95	635.5 ±21.9	645±10	642±13.6	647±14.2	646±9.4	642±17.0	646±15.7	649.5± 8.25
Thickness (mm)	6.27 ±0.05	6.34 ±0.02	6.63 ±0.21	6.29 ±0.03	6.60 ± 0.15	7.41 ± 0.05	5.71 ± 0.18	6.31±0.04	6.34±0.05	6.57±0.05	8.60± 0.2	5.90± 0.04	8.20± 0.1	6.79± 0.1	5.24±0.02
Dissolution (%)	101.02	97.2	96.94	97.45	95.12	93.53	99.53	72.65	72.65	74.48	80.52	80.38	74.90	83.33	98.2
Diameter (mm)	12.08 ±0.05	12.08 ±0.04	12.12 ±0.05	12.09 ±0.04	12.07 ± 0.01	12.09 ± 0.03	12.05 ± 0.05	12.06± 0.04	12.13± 0.08	12.18± 0.11	12.11 ±0.1	12.15 ±0.2	12.07 ±0.1	12.08 ±0.1	12.04± 0.02
Content Uniformity (%)	91.71	74.25	73.47	93.56	79.63	74.66	95.10	91.5	95.5	94.2	101.1	98.5	96	96.5	70.0

The physical properties of the formulated tablets are depicted in Table 5. The variation in weight of the formulated metronidazole tablets were consistent with Pharmacopeial specification. The tablets had well defined diameter and thicknesses with the exception of 6, 11 and 13 runs that failed both crushing and friability tests. The tablet composition resulted to this effect (Table 2). Tablet thickness has been established to vary with compressional force and density of granulation [16]. Metronidazole release was prompt with more than 70 % of drug released in 5 min. The content uniformity of all runs with the exception of runs 2, 3 and the optimized formulation were within the USP specification of 85-115% for uncoated tablets.

CONCLUSION

The linear mixture model of design expert software (ver.10) provided a basis for the assessment of effects of each and the relative effects of the three component excipients when combined in metronidazole tablet. Each of the component exhibited rapid disintegration and the combination delivered non-friable tablets (0.15 to 1.07 %) with low disintegration time (5.7 to 11.6 sec) and adequate mechanical strength (4.5 to 6.6 KgF) were KSG levels/concentrations ranged between 1.33 to 8%w/w. Although all excipients/components disintegrated the tablets rapidly, CPV was fastest and SSG was similar to KSG in this property but KSG proved to be better in delivering non-friable metronidazole tablets with adequate mechanical strength. This shows that *Khaya senegalensis* gum can be used as a super disintegrant in metronidazole tablets manufactured by direct compression and perhaps may be a solution for orally disintegrating tablets (ODT) formulations requiring mechanical strength as well as rapid disintegration with an added advantage of no special packaging due to adequate mechanical strength provided by KSG. Although, it has been mentioned that when water-swelling gums are used as disintegrants, they are effective as relatively coarse particles because the swelling of coarse particles does not form a continuous film on the tablet surface as does a finely subdivided powder [17]. Further works will be carried out to determine the actual mechanism by which this natural gum acts as a disintegrant/super disintegrant in tablet formulations.

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