Original Research Article

The Mechanical and *In Vitro* Release Properties of Diazepam from Tablets Containing Fluid Bed Dried and Lyophilized *Cocos nucifera* Microcrystalline Cellulose

ABSTRACT

Aim: This study aimed to evaluate the mechanical and *in vitro* release properties of diazepam from tablets containing fluid bed dried and lyophilized microcrystalline cellulose (MCC) obtained from the matured fruit husks of *Cocos nucifera (CN).*
Study Design: Method of experiment.
Place and Duration of Study: Department of Pharmaceutical Technology and Industrial Pharmacy, University of Nigeria, Nsukka from March 2015 to September, 2016
Methods: Dried CN fruit husks were digested in sodium hydroxide to obtain alpha (α) cellulose which on hydrolysis with mineral acid (Hydrochloric acid) solution gave *CN-MCC*. The dry MCC obtained by either fluid bed or lyophilized drying of the wet CN-MCC were coded *MCCF-Cocos* and *MCCL-Cocos* respectively. Both MCCs were used in the formulation of diazepam tablets at 20, 30 and 40 % w/w. Avicel PH 102 (AVC-102), was used as comparing standard. The tablets were evaluated for physical and dissolution properties using standard methods.
Results: Results show the tablets passed the British Pharmacopoeia specifications for weight uniformity, crushing strength, disintegration time, friability and dissolution. Diazepam tablets containing *MCCL-Cocos* (coded DCL) were mechanically stronger than those containing *MCCF-Cocos* (coded DCF). Disintegration time was in the order of DCF > DCL tablets while friability was in the order of DCL < DCF tablets. Diazepam tablets containing AVC-102 (coded DAV) were mechanically stronger than DCL and DCF tablets. The dilution potential was in the order DAV > DCL > DCF. More than 80 % of the diazepam content was released from DAV, DCL and DCF tablets.
Conclusion: Generally, DAV, DCL and DCF tablets met the British Pharmacopoeia limits for mechanical properties and *in vitro* drug release with DCL tablets showing significantly (P = .05) superior mechanical properties while DCF showed faster drug release.

Keywords: Tablets, mechanical, diazepam, Cocos nucifera, microcrystalline cellulose, dissolution

1. INTRODUCTION

The desire for enhanced drug delivery has remained a motivating factor that has driven pharmaceutical product formulators to keep searching for new excipients, active pharmaceutical ingredients (API) or methods of formulation to achieve better/optimum drug delivery from existing excipients and API. Cellulose, a plant derivative is the main structural

fiber in the plant kingdom and is known to possess remarkable mechanical properties for a polymer as its Young's modulus is estimated as roughly 130 (gigaPascal) gPa while its tensile strength is close to 1 gPa [1]. Besides this attribute, cellulose and its derivatives has over time regained prominence as a source of obtaining pharmaceutical excipients because of its natural abundance and availability, low cost, eco-friendliness, non-toxicity and ease of processing [2].

Microcrystalline cellulose, a multifunctional pharmaceutical excipient derived from cellulose has gained popularity and wide acceptance from the pharmaceutical industry because of its dry binding attributes, filler and disintegrant roles in tablet formulations [3,4]. This has made it very useful in direct compression technology of tablet manufacture. The mechanical properties of the tablets formulated with MCC have been found to vary as a result of either the pulp source or method of its preparation [4]. The source of the cellulose and the chemical treatment it is exposed to in order to derive the MCC affects the degree of crystallinity or ordered structure and other physicochemical properties of the MCC [4,5]. The degree of crystallinity is one of the major determinants of the mechanical properties of cellulose and its derivatives such as MCC [6]. It also elucidates the accessibility of the cellulose to chemical derivatization, swelling, water-binding and other factors that influence some of its physicochemical properties [7]. Besides this factor, method of drying has also been reported to affect the physical properties such as particle size, morphology, porosity, and aggregation of MCC particles [8].
Cocos nucifera fruit husk is a major agro waste found in regions of the world where the coconut plant thrives. The fruit husk is made up of the endocarp and mesocarp and is known not to be easily bio-degradable [9,10].
Diazepam is a white or yellow odourless crystalline powder of the benzodiazepine group of drugs. It is a tranquillizer that possesses anticonvulsant, sedative, muscle relaxant, and amnesic properties [11,12]. It has been gainfully employed in the treatment of anxiety conditions, as a sedative in the pre-medication treatment of muscle spasm in tetanus, alcohol withdrawal syndrome, orthopaedic and dental procedures, and endoscopy. It is the drug of choice in the management of status epilepticus where it is preferably given by the intra-venous route [12]. Its oral administration to epilepsy patients has been found to be very helpful. Routes of administration include the oral, intra - muscular, intra - venous, and rectal routes [12]. Prolonged use of diazepam could lead to the barbiturate – alcohol type of dependence [12].

The objective of this study was to apply *MCCF-Cocos* and *MCCL-Cocos* as a directly compressible excipient in the formulation of orally ingested diazepam tablets and to investigate the effects both MCCs would have on the mechanical properties of the tablets, and *in vitro* release behavior of diazepam from the tablets. Avicel PH 102 (AVC-102), a commercial brand of MCC which is usually prepared by spray drying technology was used as comparing standard.

2. MATERIAL AND METHODS

2.1 Materials

Diazepam powder (Fabrica Italiana Sintetici S.P.A., Italy, obtained from Swiss Pharma Nig. Ltd.), Sodium hydroxide (Merck, Germany), hydrochloric acid (BDH, Poole England), talc, magnesium stearate (Sigma, USA), sodium hypochlorite (JIK, Reckitt & Colman Nig. Plc), Avicel® PH 102 (FMC Biopolymer, USA). Dried chips of matured coconut fruit husk.

2.2 Methods

Some matured *Cocos nucifera* fruits from different fruiting *C. nucifera trees* within Port Harcourt, a Delta town in Nigeria were harvested, dehusked, and the husks cut into small chips and air dried. Digestion of the husk fibers in sodium hydroxide solution to obtain α cellulose and the hydrolysis of the α-cellulose using 2.5 N hydrochloric acid to obtain MCC were done. The MCC after being washed to neutrality using distilled water was squeezed through a muslin cloth to obtain a damp MCC which was divided into two portions. The fluid bed drying or lyophilization of either portion of the wet MCC was carried out. The resultant fluid bed dried MCC (coded *MCCF-Cocos*) and lyophilized MCC (coded *MCCL-Cocos*) were evaluated for their physicochemical and micromeritic properties using standard evaluation methods. Investigation and report on this have been earlier documented by Nwachukwu and Ofoefule [8]. The formulation of diazepam tablets was done using the quantities of the ingredients shown in Table 1. For each batch, the quantity of each of the ingredients was weighed and mixed in a mortar using the doubling up technique. The powder blends were evaluated for their micromeritic properties.

Table 1: Formula for diazepam tablets

Type of MCC	Ingredient/ Batch	Diazepam (mg)	Polymer (mg)	Corn starch (mg)	Magnesium stearate (mg)	Talc (mg)	Total (mg)
MCCF-Cocos	DCF-1	0.00	280.50	15.00	3.00	1.50	300.00
	DCF-2	60.00	220.50	15.00	3.00	1.50	300.00
	DCF-3	90.00	190.50	15.00	3.00	1.50	300.00
	DCF-4	120.00	160.50	15.00	3.00	1.50	300.00
MCCL-Cocos	DCL-1	0.00	280.50	15.00	3.00	1.50	300.00
	DCL-2	60.00	220.50	15.00	3.00	1.50	300.00
	DCL-3	90.00	190.50	15.00	3.00	1.50	300.00
	DCL-4	120.00	160.50	15.00	3.00	1.50	300.00
AVC-102	DAV-1	0.00	280.50	15.00	3.00	1.50	300.00
	DAV-2	60.00	220.50	15.00	3.00	1.50	300.00
	DAV-3	90.00	190.50	15.00	3.00	1.50	300.00
	DAV-4	120.00	160.50	15.00	3.00	1.50	300.00

2.3 Some micromeritic properties of diazepam powder blends

The different powder blends of the formulation containing the diazepam and the excipients as shown in Table 1 were evaluated for some of their micromeritic properties such as densities and flowability.

2.3.1 Bulk and tapped densities

The bulk density of each of the diazepam powder blends was determined by pouring 12 g of the powder into a clean dry transparent graduated 50 mL measuring cylinder kept on a flat platform. The powder in the measuring cylinder was leveled and the bulk volume noted. Replicate determinations were done for each batch of powder mix. The bulk density was determined using Equation 1:

$$\text{Bulk density } (D_b) = \frac{M}{Dv} \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad 1$$

Where M is the mass of the powder and Dv is the bulk volume.

The tapped density was determined by tapping the powder in the measuring cylinder several times on a padded flat surface until a constant volume of the powder was maintained in the cylinder during tapping. The tapped density is determined as the ratio of the mass of the powder against the tapped volume. It is expressed as shown in Equation 2:

$$\text{Tapped density } (D_t) = \frac{M}{Tv} \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad 2$$

Where M is the mass of powder and Tv is the tapped volume.

2.3.2 Angle of repose

The angle of repose (AOR) was determined for each powder blend by pouring 50 g of powder under investigation into an open-ended pipe of 3 cm diameter kept on a sheet of paper spread upon a flat platform. The cylindrical pipe was gradually pulled up and the powder formed a cone on the flat surface. Both the height of the powder heap and its diameter were measured. Replicate determinations were made. The angle of repose was determined using Equation 3:

$$\text{AOR} = \tan^{-1}\frac{2h}{d} \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad 3$$

2.3.3 Hausner's quotient and Carr's Index

The Hausner's quotient and Carr's index for the powder blends of diazepam and the excipients were calculated from Equations 4 and 5 respectively.

$$\text{Hausner's quotient (H.Q.)} = \frac{Dt}{Db} \quad \ldots\ldots\ldots\ldots \quad 4$$

$$\text{Carr's Index (C.I.)} = \left(1 - \frac{Db}{Dt}\right) \times 100 \quad \ldots\ldots\ldots \quad 5$$

Where D_b is the bulk density, and D_t is the tapped density.

2.3.4 Flow rate

A quantity of 20 g of each of the diazepam powder blends containing *MCCF-Cocos, MCCL-Cocos* and AVC-102 was poured into and allowed to flow freely from a clamped stoppered clean glass funnel whose orifice was 4 cm above a flat surface. The time taken for each of the powders to flow out of funnels orifice uninterrupted was noted. The tests were done in triplicates for all the powders and the flow rate (F.R) determined using Equation 6:

$$F.R. = \frac{M}{F.T.} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots 6$$

Where F.T. is the flow time and M is the mass of powder used.

2.4 Compaction of diazepam tablets

A total number of one hundred (100) tablets were prepared per batch at a target tablet weight of 300 mg using the formula in Table I. Four batches were formulated for each MCC. One batch (Batch I) of each of the formulations containing *MCCF-Cocos*, *MCCL-Cocos* or AVC-102 did not contain diazepam and served as the control while AVC-102 served as the standard microcrystalline cellulose powder. Direct compression of the powders into tablets was done using a single punch tablet press (Model C, Carver Inc., Winscosin, USA) fitted with a set of flat faced 10 mm stainless steel punches. All the tablets for all the batches were compressed at a uniform compression pressure of 9.81 megaPascal (mPa) and dwell time of 30 sec.

2.5 Evaluation of diazepam tablets

Each of the tablets was stored in a desiccator containing silica gel after compression and allowed a 24 h post compression relaxation time before evaluation for uniformity of weight, thickness, crushing strength, friability, disintegration, the content of active ingredient and dissolution tests.

2.5.1 Tablet physical appearance

Each tablet from each batch was examined physically for wholesomeness, odour, colour, and stains or any physical defects.

2.5.2 Uniformity of weight

Twenty tablets randomly selected from each batch of the diazepam tablets and from the different formulations of the microcrystalline cellulose powders were collectively weighed according to the British Pharmacopoeia 2012 method [13]. The mean deviation and coefficient of variation were determined. The acceptance or rejection criterion was based on the stipulation of the British Pharmacopoeia 2012 [13].

2.5.3 Crushing strength test

The crushing strength of ten diazepam tablets that were randomly selected from each batch of the different formulations was determined using a Monsanto hardness tester (Singhla Scientific Industries, India) and the value at which each tablet broke was recorded. The mean value and standard deviation were determined per batch [13].

2.5.4 Friability test

Ten tablets randomly selected from each batch of the diazepam tablets were dusted of any powder particles that may be retained on any of the surfaces of the tablet by directing a stream of air at them. They were collectively weighed and put in one of the drums of the friabilator, a model TAR 200 (Erweka®, Germany) twin drum electronic friabilator programmed to revolve at 25 rotations per minute (rpm) for 4 min. At the end of the exercise, the tablets were collected, de-dusted and any broken tablets rejected. The tablets were reweighed and the percentage abrasion resistance or friability (F) calculated from Equation 7 [14].

$$F = 100\left[1 - \frac{W}{Wo}\right] \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 7$$

Where W_o is the initial weight and W is the final weight.

2.5.5 Disintegration test

Six tablets randomly selected from each batch of the diazepam tablets were singly placed in each of the tubes of the basket of an Erweka ZT-3 (Erweka®, Germany) double basket disintegration test apparatus. The basket was put inside a beaker containing 500 mL of 0.1N HCl warmed up to 37 ± 1˚C. The oscillation speed was set at 29 ± 1 cycle per minute and the time taken for the last tablet to break up completely and pass through the mesh was noted [13].

2.5.6 Determination of wavelength of maximum absorption (λ_{max}) of diazepam

A stock solution of the pure sample of diazepam was made by weighing 100 mg of the pure sample, dissolving in 60 mL methanol in a 100 mL volumetric flask and the volume made up to the 100 mL mark with the same vehicle [15]. Serial dilutions of the stock (1.00 mg %) were made such that 0.20 mg %, 0.40 mg %, 0.60 mg %, and 0.80 mg % were obtained. Scanning of the 0.20 mg % solution was done in a JENWAY 6405 UV/vis spectrophotometer (Jenway®, England) at wavelengths ranging from 220 nm to 400 nm. The most prominent or maximum/peak absorbance (λ_{max}) was noted.

2.5.7 Standard calibration curve of diazepam

The serially diluted solutions of diazepam containing 0.20 mg %, 0.40 mg %, 0.60 mg %, 0.80 mg %, and 1.00 mg % were placed in a quartz cuvette and using the JENWAY 6405 UV/vis spectrophotometer set at a wavelength of 246 nm, the absorbance readings were taken and recorded. A plot of the concentration against absorbance readings was made and the slope determined.

2.5.8 Assay of diazepam tablet

Twenty tablets were selected at random from each batch of the diazepam tablets and were collectively weighed. They were pulverized in a porcelain mortar and an amount of powder equivalent to the weight of one tablet was taken and dispersed in 5 mL of distilled water in a 100 mL volumetric flask, and allowed to stand for 15 min. A 70 mL volume of 0.5 % v/v of sulphuric acid (H_2SO_4) in methanol was added, the mixture was shaken for 15 min and sufficient methanolic sulphuric acid solution was added to produce 100 mL. The dispersion was filtered and to 10 mL of the filtrate was added enough of the solvent to obtain a 50 mL solution. The absorbance of the resulting solution was read at 246 nm of the JENWAY 6405 UV/vis spectrophotometer [13]. The absorbance readings were correlated with the standard

calibration curve earlier established. The concentrations were determined using Beer-Lambert's Equation given as:

A = KC …………………………………… 8

Where A is absorbance, C is concentration and K is proportionality constant known as molar absorptivity.

2.5.9 Dissolution studies of diazepam

The dissolution studies of the diazepam tablets were conducted using a six station dissolution equipment model DT 600 (Erweka, Germany). The paddle method was used with each beaker containing 900 mL of 0.1 N HCl heated to a temperature of 37.0 ± 0.5˚C and a paddle speed of 100 rotations per min (rpm) [13]. One tablet was used in each beaker for the test. Five (5 mL) samples were withdrawn at 10 min intervals up to 1 h with an equal replacement with dissolution medium maintained at 37.0 ± 0.5˚C after each withdrawal. The absorbance readings of the filtrates obtained from the withdrawn samples were determined using a JENWAY 6405 spectrophotometer at a wavelength of 246 nm. The absorbance results were converted to concentrations from the calibration curve previously determined for diazepam. This was done for all the batches of the diazepam tablets.

2.5.10 Stability studies/evaluation

The different batches of the diazepam tablets were stored in airtight conditions in opaque plastic containers with tight-fitting lids at ambient conditions for a period of six months, after which they were re-assessed for degradation effects of their diazepam content.

2.5.11 Statistical evaluation

The data obtained were statistically analyzed using ANOVA and students t-test (SPSS version 21). Values were considered significant at P = 0.00 or below or equal to 0.05.

3. RESULTS AND DISCUSSION

3.1 Micromeritic properties

Some of the micromeritics data obtained from the evaluation of the different blends of diazepam powder are shown in Table 2. The tapped densities were generally higher than the bulk densities for all the batches indicating that all the MCCs being investigated were compressible. The bulk and tapped densities values were in the order DCF > DCL > DAV. The flow rate gave results between 3.05 to 5.38 g/s for DCF and DAV powders indicating weak flow behavior while DCL powders did not flow. The angle of repose of batches DCF-1 to DCF-4, DAV-1 to DAV-4 ranged between 26.43 ± 0.12 to 30.02 ± 0.23 °, and can be categorized as powders with excellent flow [13, 17]. Batches DCL-1 to DCL-3 powders with values between 34.03 ± 0.03 to 36.12 ± 0.05 ° have a good flow while DCL-4 with a value of 38.31 ± 0.33 ° is classified as a fair-flowing powder [13, 17]. The Hausner's quotient of ≤ 1.18 and Carr's index values of between 10 to 15 % possessed by batches DFC-1 to DCF-4 connotes good flow [13, 17] and correlates with the angle of repose results. Batches DAV-1 to DAV-3 had a fair flow based on the Hausner's quotient and Carr's index classification while DAV-4 had a passable flow (13, 17). Batches DCL-1 to DCL-4 also had passable flow (Table 2). Generally, a correlation of the other flow indices in Table 2 show that the DCF batches of powders were more flowable than the DAV batches while the DCL batches had

the least flow. These can be used to predict how these powders would flow from the hopper into the dies to form tablets. The DCL powders would require force feeders in tableting operations using a tableting machine to avoid improper feeding and the production of underweight and weak tablets.

Table 2: Some micromeritic properties of diazepam powder blends

Batch	Bulk density (g/mL)	Tapped density (g/mL)	Angle of repose (°)	Flow rate (g/sec)	Hausner's Quotient	Carr's Index (%)
DCF-1	0.44± 0.10	0.49 ± 0.20	26.43±0.12	5.38± 1.01	1.12 ± 0.03	10.21± 1.05
DCF-2	0.55± 0.25	0.61 ± 0.04	27.69 ± 0.03	5.26± 0.95	1.11 ± 0.02	10.70± 0.60
DCF-3	0.56± 0.05	0.64 ± 0.03	27.12 ± 0.23	4.17± 1.22	1.13 ± 0.03	11.81± 0.49
DCF-4	0.58± 0.20	0.68 ± 0.15	28.80 ± 0.17	3.98± 0.88	1.17 ± 0.06	14.64± 0.25
DCL-1	0.34± 0.01	0.44 ± 0.12	36.12 ± 0.05	N.F	1.29 ± 0.55	22.59± 0.34
DCL-2	0.35± 0.02	0.44 ± 0.01	34.03 ± 0.03	N.F	1.28 ± 0.42	22.73± 0.22
DCL-3	0.37± 0.05	0.46 ± 0.02	35.15 ± 0.02	N.F	1.27 ± 0.28	21.37± 0.31
DCL-4	0.38± 0.03	0.50 ± 0.11	38.31 ± 0.33	N.F	1.32 ± 0.35	24.30± 0.14
DAV-1	0.31± 0.50	0.38 ± 0.21	27.55 ± 0.41	3.67± 0.54	1.23 ± 0.66	18.40± 0.54
DAV-2	0.32± 0.35	0.39 ± 0.16	29.91± 0.32	3.51± 0.37	1.23 ± 0.45	18.53± 0.26
DAV-3	0.35± 0.32	0.42 ± 0.20	29.06 ± 0.22	3.55± 0.60	1.21 ± 0.35	17.58± 0.20
DAV-4	0.36± 0.25	0.46 ± 0.14	30.02 ± 0.23	3.05± 0.71	1.28 ± 0.29	22.19 ± 17

***NF** represents no flow

3.2 Evaluation of diazepam tablets

3.2.1 Uniformity of tablet weight

The results obtained for the uniformity of weight of each batch of diazepam tablets are shown in Table 3. The tablet weights were in the range of 292.95 ± 2.39 to 309.50 mg ± 1.88 %. All the tablets passed the test as they met the BP acceptance criteria for uncoated tablets weighing up to 300 mg which is given as ± 5 % variance [13,16,17]. This indicates that the powder blends were properly fed into the dies for compression and that there was a minimal variation of API content in each tablet and batch. Similarly, closer and uniform values would be obtained for other properties that have bearing with the tablet weight.

Table 3: Some physical properties of diazepam tablets

MCC	Batch	Weight uniformity [mg ± % CV]*	Crushing strength (kgF)	Friability (%)	Disintegration (min)
MCCF-Cocos	DCF-1	297.30 (1.8)	5.38 ± 0.18	0.50 ± 0.01	0.62 ± 2.25
	DCF-2	303.20 (2.54)	4.11 ± 0.15	1.05 ± 0.12	0.16 ± 0.01
	DCF-3	297.95 (2.40)	3.09 ± 0.23	1.05 ± 0.09	0.32 ± 0.03
	DCF-4	297.65 (2.59)	3.00 ± 0.21	1.50 ± 0.26	0.48 ± 0.04
MCCL-Cocos	DCL-1	292.80 (6.55)	7.16 ± 0.81	0.18 ± 0.03	1.41 ± 1.86
	DCL-2	297.20 (1.78)	5.58 ± 0.17	0.52 ± 0.01	0.29 ± 0.02
	DCL-3	292.95 (2.39)	4.89 ± 0.22	0.83 ± 0.01	0.31 ± 0.02
	DCL-4	295.55 (1.46)	4.34 ± 0.11	3.69 ± 1.38	0.52 ± 0.02
AVC-102	DAV-1	301.60 (2.48)	12.51 ± 1.12	0.56 ± 0.05	1.22 ± 0.86
	DAV-2	309.50 (1.88)	7.76 ± 0.15	0.06 ± 0.01	0.40 ± 0.02
	DAV-3	305.25 (1.83)	7.31± 0.14	0.51 ± 0.02	0.90 ± 0.28
	DAV-4	303.01(2.14)	6.16 ± 0.18	0.87 ± 0.05	1.30 ± 0.05

3.2.2 Crushing strength

The crushing strength values of the tablets (Table 3) shows that the diazepam tablets containing fluid bed dried MCC (*MCCF-Cocos*) were significantly lower (P = .028) than the lyophilized MCC (*MCCL-Cocos*) at the same compression pressure. Batches containing *MCCF-Cocos* blended with diazepam at 30 and 40 % w/w respectively (DCF-3, and DCF-4) had values below 4.00 kgF indicating mechanically weak tablets that cannot withstand the stresses expected of normal tablets [13]. Tablets containing AVC-102 had values that were higher than that obtained with lyophilized dried *C. nucifera* MCC containing diazepam (DCL) tablets in the three concentrations used. Crushing strength of all the tablet formulations containing lyophilized MCC ranged from 4.00 to 7.16 kgF which is within the acceptable value range for uncoated tablets (≥ 4.00 kgF) [13,17]. This can be explained by the higher values of porosity, low bulk and tapped densities. Thus the inter-particulate void spaces allow for a greater presence of the API while interfacing with a high level of hydrogen bonds for inter and intra mechanical bonding and interlocking which ensures a higher strength of such tablets [18]. Comparatively, amongst the three MCC powders, the commercial MCC (AVC-102) produced diazepam tablets that were mechanically strongest while *MCCF-Cocos* (Table 3) produced the weakest tablets. Thus, the physical attributes of DAV tablets are expected to be best while those of DCL tablets would be superior only to DCF tablets.

3.2.3 Disintegration

Disintegration is always regarded as an important part/quality control measure in the evaluation of normal release tablets. All the batches of tablets containing 20-40 % w/w diazepam disintegrated in less than 2 min (Table 3). The implication is that the diazepam would be readily available for dissolution as soon as it is orally ingested. Also, the formulations containing *MCCF-Cocos* and *MCCL-Cocos* behaved alike implying that drying method did not significantly (*P* =1.000) affect disintegration of the diazepam tablets. Thus, both the control and other batches containing diazepam passed the disintegration time test since the British Pharmacopoeia permits an upper limit of not more than 15 min for uncoated normal release tablets [13]. The incorporation of corn starch to the formulations could have enhanced the disintegration times obtained as corn starch is known as a good tablet disintegrant [19, 20, 21].

3.2.4 Friability

Friability values ranging from 0.06 ± 0.01 to 3.69 ± 1.38 % were obtained for the different batches of diazepam tablet (Table 3). Batches of tablets with high friability values correlated with poor crushing strength for such tablet batches while those with low friability values correlated with high crushing strengths. Most of the batches of diazepam tablets containing lyophilized MCC had friability values that were consistently lower than their fluid bed dried counterparts. This implies that the lower the friability, the higher the mechanical strength. All the batches of tablets passed the friability test except batches DCF-4 and DCL-4 that had friability values of 1.50 ± 0.26 and 3.69 ± 1.38 % respectively. The British and United States Pharmacopoeia stipulated acceptable friability value for uncoated tablets is ≤ 1 % [13,17].

3.2.5 Dilution potential

The dilution potential is an important characteristic that is quite desirous in any direct compression excipient. It can be described as the minimum quantity of excipient needed in a powder blend with an active pharmaceutical ingredient to form tablets of adequate compactibility and friability (≤ 1 %). Thus the crushing strength exhibited by each tablet batch describes its capacity to accommodate the API. From Table 3, it can be seen that tablets containing both the fluid bed dried and lyophilized dried CN-MCC had good crushing strength and friability values except batches DCF-4 and DCL-4 that failed the friability test. Batches DCF-2, DCF-3, DCL-2, and DCL-3 can be said to have a good dilution potential since these batches passed both the crushing strength and friability tests. Similarly, the AVC-102 batches (DAV-2, DAV-3, and DAV-4) met with the acceptance limit for hardness and friability for uncoated tablets and can also be assessed to have good dilution potential. Therefore, batches containing *MCCF-Cocos* and *MCCL-Cocos* can be diluted up to 30 % w/w of the total tablet weight with diazepam powder while those containing AVC-102 can be diluted up to 40 % w/w with diazepam powder. The dilution potential varies with the active pharmaceutical ingredient (API) and enables the formulation scientist or researcher to select the right combination of API and excipient in a formulation.

3.2.6 Dissolution of diazepam tablets

Figure 1 shows the dissolution or drug release from batches of diazepam tablets containing 20, 30, and 40 % w/w diazepam respectively formulated with both fluid bed dried CN-MCC (DCF-2, DCF-3, & DCF-4) and lyophilized dried (DCL-2, DCL-3, and DCL-4). The release profile of DCL (diazepam tablets containing lyophilized CN-MCC) batches was significantly lower (*P* = .045) when compared with the DCF (diazepam tablets containing fluid bed dried) batches at the same compression pressure. Within 6 min, more than 80 % of diazepam was released from DCF batches of tablets whereas it took up to 15 min for a similar release to be

observed in the DCL batch of tablets. All the batches released up to 99.25 % of their drug content within 30 min.

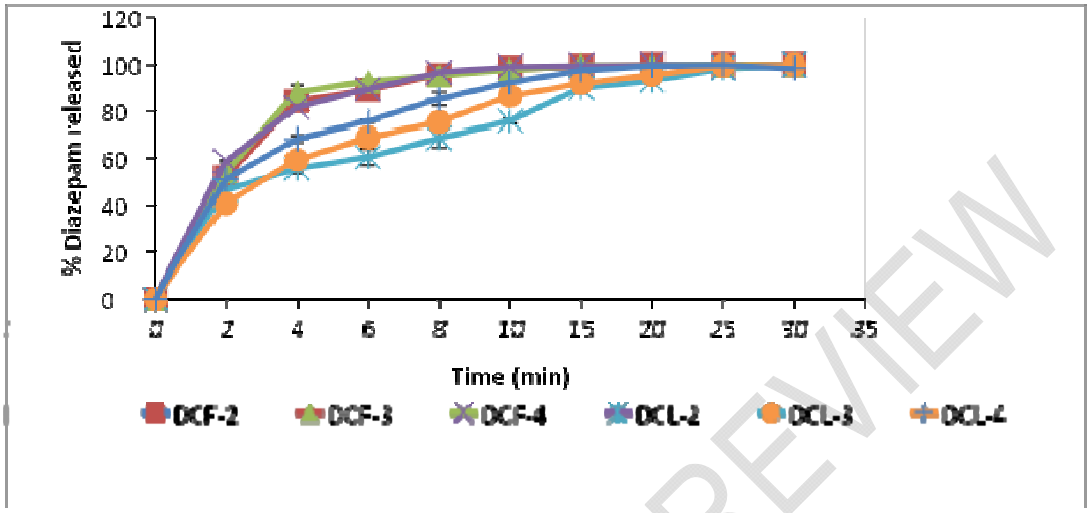

Fig. 1: Diazepam release from tablets (DCF and DCL) containing CN fluid bed dried and lyophilized MCC

Comparing the drug release between the DCF and DAV batches of tablets at all concentrations (Fig. 2), diazepam release from tablets containing AVC-102 showed drug release ranging from 36.55 to 99.98 % for the three batches containing 20, 30, and 40 % of diazepam respectively between 2 to 30 min of the release period. The drug release increased progressively as time increased. More than 80 % release occurred above 25 min in DAV-2 (20 % API formulation) while batches DAV-3 and DAV-4 containing 30 and 40 % w/w respectively of the diazepam released more than 80 % of their drug content from 15 min upward. The release behavior can be related to the disintegration characteristics of the MCCs and their high solubility in the dissolution media used. Diazepam tablets formulated with *MCCF-Cocos* exhibited good drug release behavior that was better than those formulated with AVC-102. All the formulations complied with the United States Pharmacopoeia 2009 (USP 2009) specification for dissolution or drug release for diazepam with not less than 85 % of the drug content being released within 30 min [17].

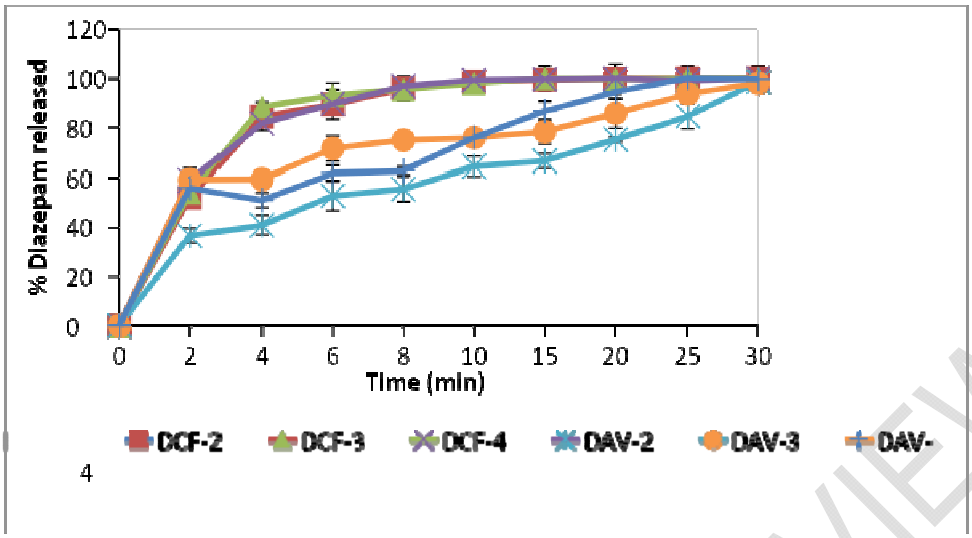

Fig.2: Diazepam release from tablets (DCF and DAV) containing CN fluid bed dried MCC and AVC-102 (DAV).

Figure 3 shows the diazepam release from DCL and DAV batches of tablets at similar concentrations. Comparatively, DCL-2, DCL-3, and DCL-4 had higher concentrations of diazepam release than that from DAV-2, DAV-3 and DAV-4 at equivalent concentrations. At 10 min, only DCL-3 and DCL-4 batches had released up to 80 % of their diazepam content. At 15 min, DCL-2 released up to 80 % of its drug content. Amongst the DAV batches, only DAV-4 had up to 80 % release within 15 min, DAV-3 met the requirement within 20 min while DAV-2 achieved that within 30 min. Thus, batches with a higher concentration of the API had up to 80 % diazepam released at lower times.

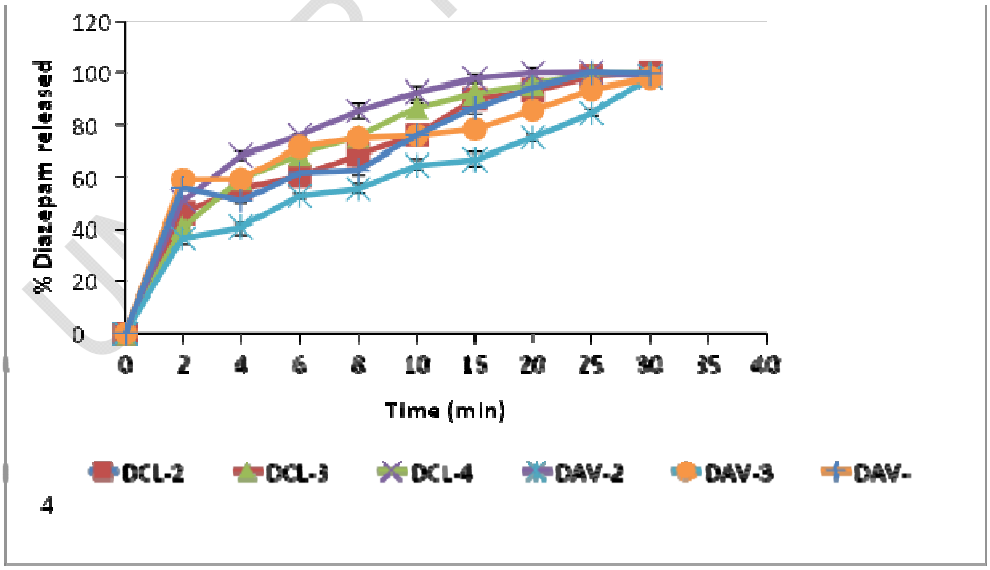

Fig. 3: Diazepam release from tablets containing lyophilized CN MCC (DCL) and AVC-102 (DAV)

3.2.7 Assay of diazepam tablets

The results of the different batches of diazepam tablets that were assayed for their content of active ingredient 48 h post-compaction are presented in Table 4. Their content of active ingredient ranged from 99.96 ± 0.20 to 100.10 ± 0.19 %. All the batches of the tablets met the compendia specifications as stated in the USP 2009 and BP 2012. The USP stipulates a lower limit of 90 % and an upper limit of 110 % while the BP states that not less than 92.50 % or more than 107.50 % of the labeled amount must be contained in the tablet [13, 17].

Table 4: Assay of diazepam tablets

S/N	Batch	Initial percent concentration (%)	Percent concentration (%) after 6 months
1	DCF-2	100.04 ± 0.11	98.26 ± 0.11
2	DCF-3	99.94 ± 0.27	99.00 ± 0.85
3	DCF-4	99.98 ± 0.11	99.28 ± 0.27
4	DCL-2	100.03 ± 0.18	98.22 ± 0.08
5	DCL-3	99.96 ± 0.20	98.88 ± 0.65
6	DCL-4	100.10 ± 0.19	99.00 ± 0.34
7	DAV 2	99.70 ± 0.61	98.25 ± 0.76
8	DAV-3	99.69 ± 0.49	99.18 ± 0.34
9	DAV-4	99.99 ± 0.01	99.45 ± 0.20

3.3 Stability studies results

3.3.1 Some physical parameters result of diazepam tablets after six months

The data obtained from some of the physical parameters such as uniformity of weight, crushing strength, disintegration time and friability of the tablets that were assessed after a six month period on the shelf are shown in Table 4.

There was slight gain in weight by the diazepam tablets formulated from each MCC which could be attributed to absorption of moisture. Microcrystalline cellulose is known to be hygroscopic [22]. However, the gain in moisture was not statistically significant (P = 1.000). Similarly, there were statistically insignificant (P =1.000) reductions in both the crushing strength and disintegration times of the diazepam tablets. It has been reported that in directly compressed tablets using two commercial brands of MCC (Hicel® 90M and AceCel® 102G), that gain in moisture did not cause any significant increase in both the crushing strength/hardness and friability of the tablets [23, 24].

The crushing strength of the diazepam tablets (Table 5) showed a slight decrease from the initial values obtained at the time of compression. All the batches passed the crushing strength test except DCF-3 and DCF-4 tablets respectively. There was no significant difference (P = 1.000) in the crushing strength of the tablets at the time of preparation and after six months of storage on the shelf.

Similarly, the disintegration time results obtained were slightly lower than at the time of preparation of the tablets. There was no significant difference (P = 1.000) in results obtained at the time of preparation of the tablets and after six months. The decrease in crushing strength values can be correlated to the lower disintegration times that were observed amongst the different batches of diazepam tablets.

The friability of the tablets showed a slight increment in value. It was found to decrease as the quantity of MCC contained in the tablet decreased and the quantity of diazepam increased. This is expected because a reduction in the crushing strength would imply weaker particle bonding within the tablets and a decrease in abrasion resistance and higher friability. There was no significant difference (P = 1.000) in the data obtained both at the time of preparation and after a six month period of storage. Generally, the diazepam tablets retained their integrity with regards to uniformity of weight, crushing strength, disintegration and friability. The data obtained for these parameters for the diazepam tablets were within the compendial limits for such tablets [13,17].

Table 5: Some physical parameters of diazepam tablets after six months

MCC	Batch	Weight uniformity [mg ± % CV]*	Crushing strength (kgF)	Friability (%)	Disintegration (min)
MCCF-Cocos	DCF-1	298.43 (1.62)	5.09 ± 0.11	0.53 ± 0.01	0.59 ± 0.82
	DCF-2	303.60 (2.55)	4.10 ± 0.15	1.10 ± 0.12	0.18 ± 0.11
	DCF-3	298.15 (2.40)	3.03 ± 0.21	1.07 ± 0.10	0.34 ± 0.03
	DCF-4	298.51 (2.57)	3.00 ± 0.21	1.55 ± 0.22	0.55 ± 0.04
MCCL-Cocos	DCL-1	293.68 (3.45)	7.01 ± 0.88	0.26 ± 0.02	1.35 ± 1.21
	DCL-2	297.90 (1.79)	5.15 ± 0.20	0.58 ± 0.01	0.27 ± 0.02
	DCL-3	293.82 (2.31)	4.51 ± 0.24	0.88 ± 0.01	0.30 ± 0.02
	DCL-4	296.61 (1.39)	4.22 ± 0.14	3.72 ± 1.36	0.25 ± 0.02
AVC-102	DAV-1	302.46 (2.49)	12.17 ± 0.89	0.59 ± 0.10	1.02 ± 0.63
	DAV-2	309.95 (1.88)	7.36 ± 0.20	0.08 ± 0.01	0.84 ± 0.02
	DAV-3	306.10 (1.81)	6.98± 0.17	0.55 ± 0.02	0.80 ± 0.21
	DAV-4	304.181(2.19)	5.86 ± 0.19	0.88 ± 0.05	0.76 ± 0.13

3.3.4 Assay results of diazepam tablets after six months.

The results of the stability studies of the diazepam tablets after six months of storage under ambient conditions showed that the tablets had maintained their integrity in the terms of content of active ingredient. The assay showed the content of active ingredient (diazepam) in the range of 99.22 – 99.42 % (Table 4). There was no significant reduction (P = .091) in the content of diazepam contained by the tablets at the time of manufacture and after a period of six months. Since tablets were stored at ambient conditions prevalent in the laboratory, the effects of hydrolysis, photolysis, thermolysis and microbial contamination/breakdown as would be experienced on the shelf in a tropical region before usage did not adversely/appreciably affect any of the preparations as the content of diazepam contained was within the acceptable BP 2012 or USP 2009 limits for diazepam tablets [13,17]. Thus, the *MCCF-Cocos, MCCL-Cocos*, AVC-102 and the other excipients used in the formulation of the drug did not cause any significant deterioration of the drug. Also, the physical inspection of the tablets did not show any discoloration or spotting that could be suggestive of microbial contamination.

3.3.5 Dissolution results after six months

Figures 4 – 6 show the result of the dissolution or diazepam release from the tablets formulated with the different MCCs. The diazepam release from the tablets followed a similar pattern to what was observed at the time of production of the tablets as shown in Figures 1-3. There were slight decrements in the percentage of diazepam released for each batch when compared to the initial dissolution values obtained. However, these differences were statistically insignificant (P = 1.000). The percentage of diazepam release for all the batches of tablets were within the stipulations of the BP and USP 2009 [13, 17]. It was observed that the tablets containing the fluid bed dried MCC had higher drug release than those containing the lyophilized MCC and AVC-102.

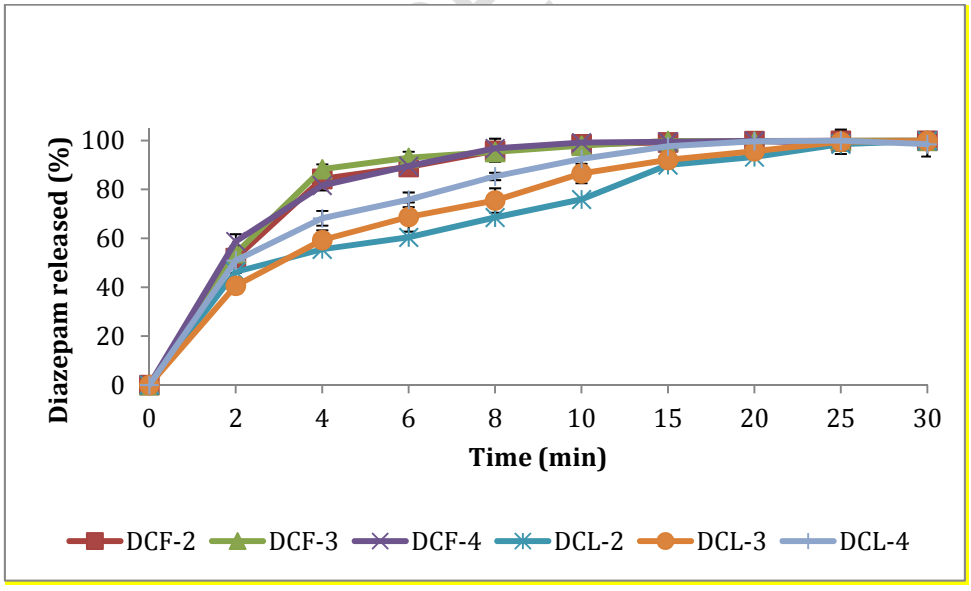

Fig.4: Diazepam release from DCF and DCL tablets after six months

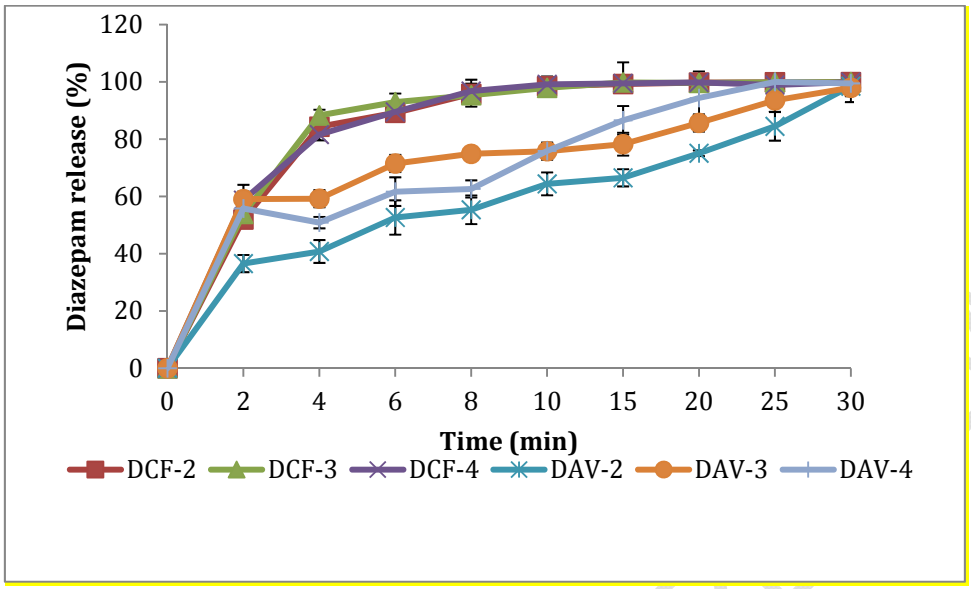

Fig.5: Diazepam release from DCF and DAV tablets after six months

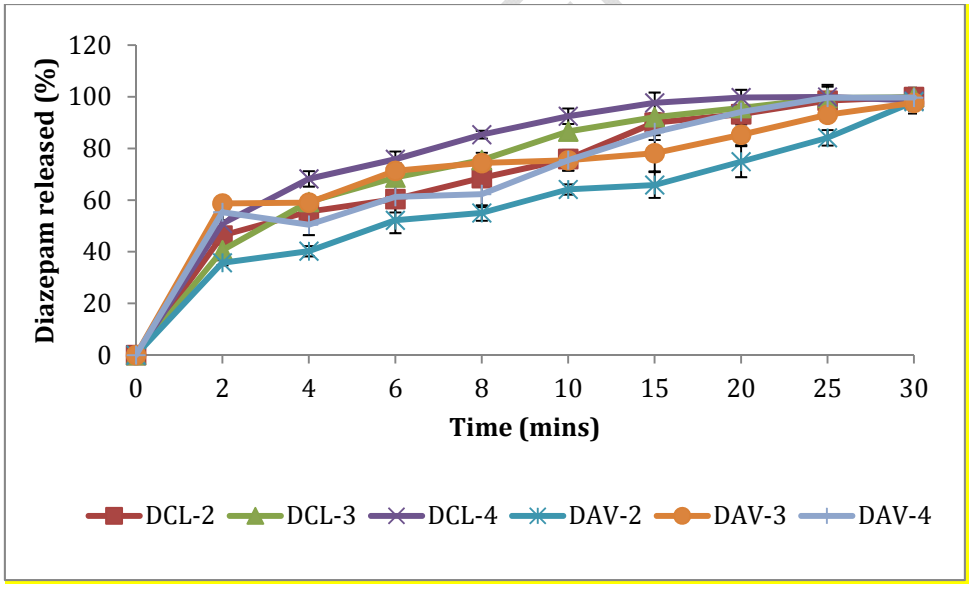

Fig.6: Diazepam release from DCL and DAV tablets after six months

4.0 CONCLUSION

The powder blends of the diazepam formulations containing the MCCs showed good densification and compressibility behavior. The formulations containing *MCCF-Cocos* showed better flow properties than those containing AVC-102 and *MCCL- Cocos.* The diazepam tablets formulated with the CN MCCs generally showed minimal weight variation. The diazepam tablets containing the lyophilized *C. nucifera* MCC (DCL-2, DCL-3, and DCL-4) showed higher crushing strength and disintegration times than those containing fluid bed dried MCC (DCF-2, DCF-3 and DCF-4) while the DCF batches had higher friability values. These imply that the DCL batches of tablets were mechanically stronger than the DCF batches. Diazepam tablets containing AVC-102 (DAV) showed higher mechanical strength than those containing the CN MCCs. Disintegration times and dissolution were more enhanced in the DCF batches than the DCL and DAV batches. The mechanical properties, disintegration and dissolution properties of all the tablets were, however, within the specified limits stated in the British Pharmacopoeia both at the time of tableting and six months post tableting. Considering the dilution potential of both MCCs, it was observed that the best mechanical attributes existed at 30 % w/w diazepam content (DCL-3 and DCF-3). There was no appreciable degradation in their mechanical properties and diazepam content after six months on the shelf. Both *MCCF-Cocos* and *MCCL- Cocos* proved to be good excipients for the formulation of diazepam tablets, although diazepam tablets containing *MCCL- Cocos* were mechanically stronger while those containing *MCCF-Cocos* had a faster drug release.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

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COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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