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Application of Microcrystalline Cellulose Powders Obtained from *Gossypiumherbaceum* As Dry Binder in the Formulation of Diazepam Tablets

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ABSTRACT

Background: Microcrystalline cellulose (MCC) is a popular dry binder in tablet formulation. Differences in its processing methods can significantly affect its tableting properties.

Aim: Assessment of the tableting and *in-vitro* release properties of diazepam tablets formulated with *Gossypiumherbaceum* (GH) derived MCC that was dried by two different methods.

Methods: *G.herbaceum* bolls were de-lignified in sodium hydroxide solutions to obtain α-cellulose which was hydrolyzed with 2.0 N hydrochloric acid to obtain MCC. The neutralized damp MCC was separated into two portions. One portion was fluid bed dried (*MCC-GossF*) while the other portion was lyophilized (*MCC-GossL*). Diazepam tablets were prepared with 20, 30 and 40%w/w of *MCC-GossF* and *MCC-GossL*..Avicel PH 102 (AVH-102) served as comparing standard. The formulations were evaluated using standard methods.

Results: The powders flowed well and the tablets met with British Pharmacopoiea specifications. Diazepam tablets containing *MCC-GossL* (DGL) were stronger than those of *MCC-GossF* (DCF) ($p<0.05$). The disintegration times were < 2 min and friability $\leq 1\%$. The strength of tablets containing AVH-102 (DAV) compared well with those of DGL tablets. More than 80% of diazepam was released from the tablets.

Conclusion: The GH MCCs served as good dry binders in the formulation of diazepam tablets.

1. Introduction

Solid compacts represented by compressed tablets remain one of the most acceptable and prescribed oral solid dosage forms in use today. Ordinarily tablets are made up of a combination of the active pharmaceutical ingredient (API) different excipients which besides acting as carriers for the API, but can also enhance its therapeutic effect, or efficacy (Singh *et al.*, 2014; Meuus, 2011; Mothilai *et al.*, 2012). The pharmaceutical formulators concerns, amongst others, include that the tablets produced must have enough strength to withstand the stresses of transportation, packaging, storage and handling as well as have the ability to disintegrate and release its active pharmaceutical ingredient (API) in a predictable, reproducible and desirable manner when orally ingested (Mothilai *et al.*, 2012; Kunnath *et al.*, 2018). Amongst the three major methods used in the preparation of granules for compression of tablets, the direct compression technology is gaining eminence as a result of the obvious advantages it has over the other two methods-dry granulation and wet granulation (Gohel, 2014). Dry binders are desirable in direct compression technology as moisture and heat are avoided at all stages of manufacture. This gives obvious advantage to the APIs that are highly unstable as a result of exposure to a certain degree of moisture, heat and light (Mollan & Celik, 1995).

Cellulose is the major component of the cell structure of most green plants (Gibson, 2012; Hindi & Abohassan, 2016). It exists in the cell wall alongside hemicellulose and lignin and imparts physical strength and shape to the plant. Microcrystalline cellulose, MCC, a pure and partially depolymerized form of cellulose is derived commercially from the pulp of wood (soft and hard woods), non woody sources and agricultural wastes (Chaerunisaa, 2017). The following plants have been sources of its derivitization: cotton linters, stalk and hosiery (Rashid *et al.*, 2017; Ohwoavworhua & Adelakun, 2005; Chauhan 2009; Chuayjuljit *et al.*, 2010), groundnut seed husks (Ohwoavworhua *et al.*, 2009), water

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hyacinth (Gaonkar & Kulkarni, 1987; Suryadi *et al.*, 2017), papaya stem (Nwajiobi *et al.*, 2019), banana stem (Emeje *et al.*, 2020), sugarcane stem peels and bargasse (Nwachukwu & Ugoeze, 2018; Nwachukwu *et al.*, 2018; Ugoeze & Nwachukwu, 2018), orange mesocarp (Ejikeme, 2008), corn cob (Suvachittanont & Ratanapan 2013; Azubuike *et al.*, 2012), soybean husk (Uesu *et al.*, 2000), coconut fruit husk (Gaonkar & Kulkarni 1989; Nwachukwu and Ofoefule, 2017), oil palm biomass residue (Haafiz, 2013), oil palm fronds (Owolabia *et al.*, 2017), and rice husk (Mollan & Celik, 1995; Suryadi *et al.*, 2017). It has been reported that the quality of MCC obtained can be affected by the botanical source of the pulp since variations exist in the chemical content (quantities of lignin, cellulose and hemicellulose) as well as the organizational arrangement of different plants. These cause differences in the composition of the alpha cellulose as well as the crystallinity and arrangement of the MCC obtained (Emeje *et al.*, 2020; Ilindra & Dhake, 2008; Ohwoavworhua & Adelakun, 2005). Cellulose occurs in the purest and highest quantities in cotton linters (Barauh *et al.*, 2000).

Commercially, cotton linter may be considered as the most economically treasured fibre of plant origin globally. Its commercial application in the textile industry, include in the manufacture of fabrics either alone or in combination with other plant, animal or synthetic fibers (Anand & Chawla, 1981). Amongst the variety of products derived from cotton fiber are sewing thread, upholstery for automobiles, paper, fishing net, film for photography and explosives. Oil extracted from the seeds of cotton has been useful in the culinary industry such as in the preparation of margarine, cooking and frying of food items, manufacture of soap, mayonnaise as well as cosmetic products and lubricants. The oil is also used in diesel engines as biofuel (Yalli *et al.*, 2014). Cotton is processed to obtain different types of cellulose which can be chemically modified to obtain cellulosics such as methylcellulose, sodium carboxymethylcellulose, ethyl cellulose, hydroxypropylcellulose, hydroxypropyl methyl cellulose and micro crystalline cellulose (Klemm *et al.*, 2005). The pharmaceutical industry applies these cellulose derivatives in the formulation of different kinds of liquid, semi-solid and solid dosage forms where they serve as viscosity enhancers, fillers/diluents, binders and as disintegrants (Yalli *et al.*, 2014).

Diazepam is a benzodiazepine class of tranquillizer that is clinically employed in the management of convulsion because of its muscle relaxant property. It is also used as a sedative in the management of patients suffering from anxiety, pre-medication in the management of muscle spasm caused by tetanus, endoscopy, dental and orthopedic procedures. When orally ingested, it is wholly absorbed from the gastro intestinal tract and can be observed to be maximally available in the plasma within 30-60 min (Sweetman, 2011). The rate of absorption is affected by the age of the patient and a delay in its absorption in geriatrics has been reported (BNF 73, 2007). The attainment of the peak plasma concentration depends on the route through which the diazepam is administered. The popular routes of administration are the oral, intra-muscular, intra-venous, and rectal routes. When administration is through the intra muscular route, an erratic absorption and lower plasma concentration is observed compared to the oral route. Diazepam has high lipid solubility as well as a biphasic half-life. The first phase occurs rapidly while the second phase takes between 24-48 h after administration.

Since the oral route offers a more stable absorption and higher peak plasma concentration of diazepam, formulations of diazepam tablets for oral administration which contained fluid bed dried (MCC-GossF) and lyophilized *G. herbaceum* MCC (MCC-GossL) were prepared and the effects of both MCCs on the mechanical and *in vitro* release properties of diazepam investigated.

2. Materials and Methods

2.1. Materials

Matured *G. herbaceum* linters (locally sourced from cotton farmers in Katsina, Nigeria), Diazepam powder (donated by 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), distilled water.

2.2. Methods

2.2.1. Processing of microcrystalline cellulose

The processing of *Gossypiumherbaceum* linters to produce microcrystalline cellulose has earlier been reported (Nwachukwu & Ofoefule, 2020; Ofoefule *et al.*, 2017). Traces of oils and waxes were removed from the cotton wool by submerging 500 g of it in ethanol (95 % v/v) for a period of 12 h after which the alcohol was drained off. The GH linters was boiled at a temperature of 100 °C for 3 h in a solution of 2.5 % w/v sodium hydroxide. It was washed with distilled water until neutral to litmus, bleached with a solution of sodium hypochlorite (0.4 % w/v) at 80 °C for 30 min, further washed with distilled water until it was neutral to litmus. It was further digested by boiling at 100 °C for 1 h in a solution of NaOH (17.5 % w/v) and bleached with sodium hypochlorite solution (0.4 % w/v) to obtain alpha (α) cellulose. Subsequent heating of the oven dried α-cellulose in a solution of 2.0 N hydrochloric acid at a temperature of 105

°C for 15 min resulted in the conversion of the α-cellulose into microcrystalline cellulose (MCC). The neutralized wet MCC that was obtained by washing off the HCL with distilled water was divided into two portions. One of the portions was dried using fluid bed dryer at a temperature of 60 ± 1°C and inlet air of 30 m^3 min^{-1} for 3 h (Sherwood® Tonado model, China). The other portion was dried by lyophilization at a temperature of – 45 °C for 6 h (Gallenkamp®, model LGT 18, England). The fluid bed dried MCC was labelled *MCC-GossF* while the lyophilized MCC was labelled *MCC-GossL*. Milling of the MCCs were done using a blender (Binatone, Japan) and the particles passed through a 250 µm stainless steel sieve (Retsch®, Germany). The physicochemical, flow and compaction properties of these MCCs have earlier been reported by Nwachukwu and Ofoefule (Nwachukwu and Ofoefule, 2020).

2.2.2. Formulation of diazepam tablets

The formula for the preparation of the diazepam tablets is shown in Table 1. The ingredients in each formulation batch were homogeneously blended.

Table 1: Formula for diazepam tablets.

Ingredient/ Batch	Diazepam (mg)	Polymer (mg)	Corn starch (mg)	Magnesium stearate (mg)	Talc (mg)	Total (mg)
DGF-1	0.00	280.50	15.00	3.00	1.50	300.00
DGF-2	60.00	220.50	15.00	3.00	1.50	300.00
DGF-3	90.00	190.50	15.00	3.00	1.50	300.00
DGF-4	120.00	160.50	15.00	3.00	1.50	300.00
DGL-1	0.00	280.50	15.00	3.00	1.50	300.00
DGL-2	60.00	220.50	15.00	3.00	1.50	300.00
DGL-3	90.00	190.50	15.00	3.00	1.50	300.00
DGL-4	120.00	160.50	15.00	3.00	1.50	300.00
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. Evaluation of Diazepam Formulations

2.3.1. Micromeritic properties

Some micromeritic properties (densities and flow behavior) of the diazepam formulations were investigated.

2.3.1.1. Bulk and tapped densities

Determination of the bulk density of each diazepam formulation was done by pouring 15 g of the powder into a graduated 50 ml measuring cylinder rested on a flat table and the volume of the powder taken as the bulk volume. Three replicate tests were carried out and bulk density was determined using Equation 1 (Ansel *et al.*, 2005):

Bulk density = (mass of powder)/(bulk volume of powder) (1)

The agitation by tapping of powder in the measuring cylinder on the padded flat surface until there was no further reduction in volume was read as the tapped volume and the tapped density calculated using Equation 2 (Ansel *et al.*, 2005).

Tapped density = (mass of powder)/(tapped volume of powder) (2)

2.3.1.2. Angle of repose

Determination of the angle of repose (AOR) was done by pouring 20 g of the formulated diazepam powder into an vertically placed open ended cylindrical pipe of dimension (60 cm length and 3 cm diameter) kept on a upon a flat table. The height and diameter of the heap of powder formed on the table after the pipe was gradually pulled up were measured. Three replicate tests were carried out. The

angle of repose was determined by fitting the data obtained into Equation 3 (Mistry *et al.*, 2017).

$$AOR = tan - 1 \quad 2h/d \tag{3}$$

2.3.1.3. Hausner's quotient and Carr's Index

Determination of the Hausner's quotient and Carr's index for the diazepam formulations were achieved by fitting the data obtained for bulk density (D_b) and tapped density (D_t) into Equations 4 and 5 respectively (Staniforth, 1988).

$$Hausner's\ quotient\ (H.Q.) = Dt/Db \tag{4}$$

$$Carr's\ Index\ (C.I.) = (1 - Db/Dt)x\ 100 \tag{5}$$

2.4. Compaction of Diazepam Tablets

The different blends of diazepam formulations (Table 1) were tableted using a single punch hydraulic tablet press (Model C, Carver Inc., Winscosin, USA). Tableting was done at compression load of 9.81 megaPascal (mPa), dwell time of 30 sec and target weight per tablet of 300 mg.

2.5. Evaluation of Diazepam Tablets

The diazepam tablets were allowed to relax 24 h after tableting before they were physically inspected and evaluated for variation in weight, hardness, friability, disintegration time, content of active ingredient and dissolution tests.

2.5.1. Tablet physical appearance

Tablets from each batch were examined physically for odor, color, stains or any physical defects.

2.5.2. Uniformity of weight

A total of twenty diazepam tablets were randomly selected from every batch of the formulations and weighed together according to the BP 2012 method(BP, 2012). The average weight, standard deviation and coefficient of variation were calculated.

2.5.3. Hardness/ crushing strength test

The crushing strength of ten randomly selected diazepam tablets from every batch of the formulations was determined with a hardness tester, model TBH 100 (Erweka, Germany) and the value at which each tablet broke was recorded. The average crushing strength for each batch and standard deviation were determined (BP, 2012).

2.5.4. Friability test

Ten diazepam tablets were randomly selected from every batch and any adhering powder or particle on the tablet removed by exposing it to a jet of air emitted from a hand drier machine. After weighing the tablets together, they were put in the drum of a friability test machine, model TAR 200 (Erweka®, Germany) set to rotate at a speed of 25 revolutions per minute (rpm) for 4 min. On completion of the process, the tablets were collected, de-dusted and reweighed collectively. Tablets that broke into two halves were rejected as bad and not weighed. The percentage friability (F) was calculated using Equation 6 (Armstrong, 1990).

$$F = [(W_0 - W)/W_0]\ x\ 100 \tag{6}$$

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

2.5.5. Disintegration test

Six diazepam tablets randomly chosen from each batch of the formulation was used. One tablet was put into each cylindrical tube of the basket of a model ZT-3 (Erweka®, Germany) double basket disintegration test machine. The machine was set to heat up to 37 ± 1°C with the oscillation speed set at 29 ± 1 cycle per minute (cpm). The basket containing the tablets was dipped into a 500 ml solution of 0.1N HCl held in a 1 L beaker. The time that it took the last tablet to break up completely and pass through the mesh was noted (BP, 2012).

2.5.6. Standard calibration curve of diazepam

A stock solution of diazepam was prepared by weighing 100 mg of the pure diazepam powder into 60 ml of methanol contained in a 100 ml volumetric flask. The volumetric flask was shaken to dissolve the diazepam and was made up to the 100 mL mark with the methanol (BP, 2012).The stock solution was serially diluted to obtain concentrations of 0.20 mg %, 0.40 mg %, 0.60 mg % and 0.80 mg %. Scanning of the 0.20 mg % solution was done in a model 6405 UV/vis spectrophotometer (Jenway®, England) at wavelengths ranging from 220 to 400 nm to obtain the maximum/peak absorbance (λ_{max}) at 246 nm**.** The 0.40 mg %, 0.60 mg %, 0.80 mg % and 1.00 mg % solutions were placed in a quartz cuvette and their absorbance's determined. A plot of the concentrations against absorbance readings was made and the slope determined.

2.5.8. Assay of diazepam tablet

Twenty diazepam tablets selected at random from each batch of the formulation were weighed together, pulverized in a porcelain mortar to fine powder and a quantity equal to the weight of one tablet was taken and dispersed in 5 ml of distilled water in a 100 ml volumetric flask which was allowed to stand for 15 min. A volume of 70 ml of 0.5 % v/v of sulphuric acid (H_2SO_4) in methanol was added, the mixture

was shaken for 15 min and sufficient methanol in sulphuric acid solution was used to make up the volume to 100 ml. The dispersion was filtered and 10 ml of the filtrate was measured out and diluted with the methanol-sulphuric acid solution to obtain a 50 ml preparation (BP, 2012). The absorbance of the filtrate was read at 246 nm wavelength of the JENWAY 6405 UV/vis spectrophotometer. The absorbance's obtained for the tablets from the different batches were correlated with the standard calibration curve earlier established and their concentrations determined using the Beer Lambert's Equation which is stated as (Armstrong, 1990):

$$A = KC \quad (7)$$

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 of diazepam from the tablet formulations was investigated using the BP apparatus II method [18]. A six station model DT 600 (Erweka, Germany) containing 900 ml of 0.1 N HCL in each of the six beakers was set to operate at bath temperature of 37.0 ± 0.5˚C and paddle speed of 100 rotations per min (rpm) (Emeje *et al.*, 2020). A single tablet was introduced into each beaker for the test and 5 ml of the sample was withdrawn at 2, 4, 6, 8, 10, 15, 20, 25 and 30 min. After each withdrawal, 5 ml of the dissolution medium maintained at the bath temperature of 37.0 ± 0.5˚C was introduced into the beaker. The withdrawn samples were filtered and the absorbance determined with the aid of a model 6405 spectrophotometer (JENWAY, UK) at a wavelength of 246 nm. The absorbance readings were fitted into the standard calibration curve equation for diazepam which had been established earlier in order to calculate the concentration of diazepam it contained.

2.6. Kinetics and Mechanism of Diazepam Release

The kinetics and mechanism of diazepam release from the tablets were evaluated by fitting the dissolution data obtained into zero order, first order, Higuchi square root kinetics and Korsmeyer-Peppas models (Korsmeyer & Peppas 1981; Achor *et al.*, 2014).

2.7. Statistical Analysis

The statistical analysis of the data obtained was done using one way analysis of variance (ANOVA) with the aid of an IBM SPSS version 21 software (IBM, Chicago, USA). Values were considered significant at 95 % confidence interval or $p < 0.05$.

3. Results and Discussion

3.1. Micromeritic Properties

Table 2 shows some of the micromeritic results obtained from the evaluation of the different diazepam in MCC blends. Generally, there was an increase in the bulk and tapped densities of the powder blends as the quantity of

Table 2: Some micromeritic properties of diazepam powder formulations.

Batch	Bulk density (g/mL)	Tapped density (g/mL)	Angle of repose (°)	Flow rate (g/sec)	Hausner's Quotient	Carr's Index (%)
DGF-1	0.41 ± 1.20	0.50 ± 0.33	28.52 ± 0.25	3.63 ± 1.05	1.21 ± 0.27	18.01 ± 0.30
DGF-2	0.45 ± 0.97	0.55 ± 0.21	29.07 ±0.30	3.42 ± 1.00	1.22 ± 0.23	18.18 ± 0.25
DGF-3	0.47 ± 1.05	0.58 ± 0.17	29.68 ± 0.18	3.35 ± 0.88	1.23 ± 0.18	18.36 ± 0.21
DGF-4	0.39 ± 0.83	0.49 ± 0.19	30.03 ± 0.22	3.06 ± 1.20	1.25 ± 0.19	20.41 ± 0.22
DGL-1	0.36 ± 0.68	0.50 ± 0.17	38.35 ± 0.14	NF	1.38 ± 0.11	28.00 ± 0.40
DGL-2	0.39 ± 0.80	0.56 ± 0.20	36.22 ± 0.10	NF	1.43 ± 0.14	26.42 ± 0.24
DGL-3	0.37 ± 0.65	0.51 ± 0.25	37.14 ± 0.20	NF	1.37 ± 0.10	27.45 ± 0.35
DGL-4	0.35 ± 0.75	0.53 ± 0.23	39.05 ± 0.16	NF	1.51 ± 0.22	33.36 ± 0.22
DAV-1	0.31 ± 0.64	0.38 ± 0.12	29.55 ± 0.12	3.67 ± 0.90	1.23 ± 0.15	18.40 ± 0.15
DAV-2	0.32 ± 0.70	0.39 ± 0.15	29.91 ± 0.10	3.51 ± 1.20	1.23 ± 0.12	18.53 ± 0.22
DAV-3	0.35 ± 0.54	0.42 ± 0.13	29.06 ± 0.11	3.55 ± 0.95	1.21 ± 0.11	17.58 ± 0.42
DAV-4	0.36 ± 0.61	0.46 ± 0.10	30.02 ± 0.10	3.05 ± 1.02	1.24 ± 0.19	22.19 ± 0.32

NF represents no flow.

diazepam contained in the blends increased. All the batches that did not contain diazepam (control batches) had the lowest bulk and tapped density values. Amongst the control batches, the order of these densities were DGF–1 > DGL–1 > DAV–1. Similarly, amongst the batches of powder blends that contained diazepam, the order of the bulk and tapped densities were DGF > DGL > DAV. The bulk densities were lower than the tapped densities which imply volume reduction of the different powder blends as a result of tapping. This shows that the powders are compressible (Achor *et al.*, 2014). The flow rate values of 3.35 to 3.67 g/s obtained for the DGF and DAV batches show that the powders do not have a good flow. The DGL powder blends did not flow (Table 2). Flow rate of the powders reduced as the quantity of diazepam contained in the batch increased. This is as a result of the cohesive nature of diazepam powder. The angle of repose values of DGF and DAV (Table 2) powders classify them as excellent flowing while DGL had a passable flow (BP, 2012). Based on the Hausner's quotient, the DGF and DAV powders have a fair flow as their values ranged from 1.21 ± 0.11 to 1.25 ± 0.19 while the DGL powders ranged from 1.37 ± 0.10 to 1.51 ± 0.22 which is indicative of poor flowability (Table 2) (Staniforth, 1988). The Carr's index parameter of flow determination (Table 2) show that all the batches of DGF powder formulation, DAV-1 to DAV-3 powders had a fair flow (16-20 %), and DAV-4 had a passable flow while DGL batches of powder had a very poor flow (32-37 %) (BP, 2012).

3.2. Evaluation of Diazepam Tablets

3.2.1. Physical inspection of tablets

The result of the physical inspection of the tablets for defects such as oil stains, chipping, capping, breakages or any other physical defect showed that there was no defect.

3.2.2. Uniformity of weight

The weights of the different batches of tablets are shown in Table 3. The weights of the tablets ranged from 297.50 ± 0.21 to 309.50 mg ± 1.88 % and were within the British Pharmacopoeia specification for uniformity of weight of uncoated tablets (BP, 2012).

3.2.3. Hardness

The hardness of the diazepam tablets ranged from 49.91 ± 0.10 to 76.10 ± 0.17 N while the control batches which did not contain diazepam ranged from 143.37 ± 1.34 to 246.54 ± 2.36 N (Table 3). The control batches were significantly stronger ($p < 0.05$) than the tablets that contained diazepam. The hardness of the tablets decreased as the quantity of diazepam contained by the tablets increased. At similar diazepam and MCC concentrations, tablets containing MCC-GossL were significantly stronger ($p < 0.05$) than those containing MCC-GossF but compared favourably with tablets containing AVH-102 (Table 3). However, all the diazepam tablets met with the British Pharmacopoeia specification for the hardness test for uncoated tablets which is given as ≥ 39. 23 N (BP, 2012). Complying with this criterion qualifies them as strong tablets that can withstand the stresses of handling such as strip packaging and transportation.

3.3.4. Disintegration

The disintegration times results of the tablets are shown in Table 3. The disintegration times of the tablets containing diazepam were lower than the control batches. All the batches of diazepam tablets disintegrated within 2 min. This implies that their diazepam content would be available for dissolution and absorption very easily upon oral ingestion. This is a desirable feature because diazepam is mainly used as an emergency drug for central nervous system disorders especially where the parenteral route is not possible. All the batches of tablets complied with the BP specification for disintegration which is given as ≤ 15 min for uncoated tablets (BP, 2012).

3.3.5. Friability

The results of the friability evaluation of the diazepam tablets are shown in Table 3. The friability of the control batches of each MCC was lower than the corresponding batches containing diazepam. The friability values increased as the quantity of diazepam contained by the tablet increased. The trend was similar for the three MCCs used. The friability values of the tablets containing MCC-GossL were lower than those of MCC-GossF (Table 3). The result obtained is expected as DGL tablets were mechanically stronger than DGF tablets. All the batches had friability of < 1 % except DGF-4. Based on both the British Pharmacopoeia and United States Pharmacopoeia (USP) specification that uncoated tablets should have friability values of ≤ 1 %, all the batches of diazepam tablets passed the friability test except DGF-4 (BP, 2012; USP, 2009). All the batches, except DGF-4, are not expected to crumble or show surface deformity as a result of abrasion during handling, packaging and transportation.

3.3.6. Assay of diazepam tablets

The assay or content of diazepam in the tablets at the time of formulation is shown in Table 3. The control batches did not contain diazepam. The other batches of diazepam tablets were found to contain diazepam in the range of 99.04 ± 0.96 to 100.26 ± 0.25 %. The content of diazepam in

Table 3: Some properties of diazepam tablets.

Batch	Weight uniformity [mg± CV(%)]	Hardness ± SD (N)	Friability ± SD (%)	Disintegration ± SD (min)	Hardness –Friability Ratio (H-FR)	Concentration diazepam (%)
DGF-1	297.50 ± 0.21	143.37 ± 1.34	0.47 ± 0.05	1.19 ± 0.02	305.04	0.00 ± 0.00
DGF-2	305.25 ±1.89	67.78 ± 0.27	0.72 ± 0.01	0.12 ± 0.03	94.14	100.28 ± 0.25
DGF-3	300.70 ± 2.95	60.80 ± 0.34	0.87 ± 0.04	0.18 ± 0.03	69.84	99.04 ± 0.96
DGF-4	299.00 ± 2.15	49.91 ± 0.10	1.29 ± 0.67	0.28 ± 0.03	38.64	99.16 ± 0.24
DGL-1	299.60 ± 3.22	194.07 ± 1.52	0.42 ± 0.01	3.34 ± 0.17	462.07	0.00 ± 0.00
DGL-2	301.20 ± 2.73	80.71 ± 0.32	0.39 ± 0.03	0.87 ± 0.25	206.35	99.40 ± 0.54
DGL-3	299.70 ± 2.27	72.08 ± 0.32	0.58 ± 0.01	1.12 ± 0.09	144.16	99.91 ± 0.28
DGL-4	293.75 ± 1.59	68.64 ± 0.76	0.76 ± 0.01	0.12 ± 0.19	90.32	99.90 ± 0.28
DAV-1	301.60 ± 2.48	246.54 ± 2.36	0.42 ± 0.05	10.22 ± 0.86	587.00	0.00 ± 0.00
DAV-2	309.50 ± 1.88	76.10 ± 0.17	0.60 ± 0.01	0.40 ± 0.02	126.33	99.70 ± 0.61
DAV-3	305.25 ± 1.83	71.78± 0.26	0.71 ± 0.02	0.90 ± 0.28	101.80	99.69 ± 0.49
DAV-4	303.01 ± 2.14	70.32 ± 0.26	0.87 ± 0.05	1.30 ± 0.05	80.83	99.99 ± 0.01

these tablets complied with the BP and USP specification for diazepam tablets. The BP states that not less than 92.50 % or more than 107.50 % of the labeled amount must be contained in the tablet while the USP stipulates a lower limit of 90 % and an upper limit of 110 % (BP, 2012; USP, 2009). Based on these compendia specifications, all batches of the diazepam tablets passed the content of active ingredient test.

3.4. Dilution Potential

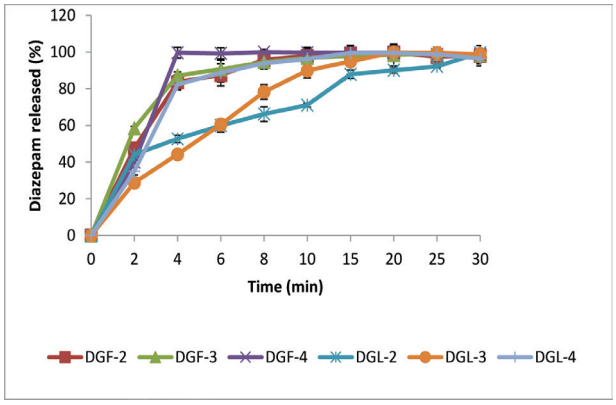
The carrying capacity of an excipient is its ability to be diluted with a certain quantity of the active pharmaceutical ingredient (API) and yet it would have the physical characteristics of the tablets formed conforming to acceptable pharmacopoeia standards. In direct compression technology, the particle size of both the excipient and the API play a prominent role. When the particle sizes are similar, the excipient presents a large number of attachment points for the API and thus could contain a high quantity of the API. The major index that helps in the assessment of the dilution potential of tabletsis the crushing strength/hardness and friability behavior of the tablets. The maximum dilution potential is regarded as that concentration of the API that can be contained in the tablet for it to pass the hardness and the friability tests respectively. The DGF, DGL and AVH-102 tablets met with the BP, USP specifications for hardness and friability except batch DGF-4 where the friability was 1.29 ± 0.67 %. Both DGL and DAV had dilution potential up to 40 % while DGF had up to 30 %. This agrees with the hardness-friability ratio (H-FR) index assessment shown in Table 3. Since hardness of $\geq$ 39.23 N and friability of $\leq$ 1 % are the set limits (BP, 2012), it implies that H-FR of $\geq$ 39.23 is the bench mark of determining physically strong tablets. All the tablet batches shown in Table 3 had H-FR values that were higher than 39.23 except for batch DGF-4 that had a value of 38.64. Thus, the DGF tablets can be diluted up to 30 % (DGF-3) whereas DGL and DAV batches can be diluted up to 40 % (DGL-4 and DAV-4).

3.5. Dissolution Profile

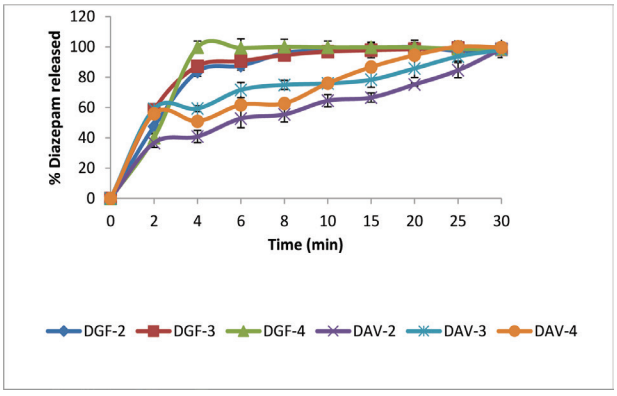
Results of the dissolution or diazepam release from the tablets are shown in Figures 1-3. The diazepam tablets containing DGF-4 was released up to 99.66 % at 4 min, and was followed by DGF-3 and DGF-2 tablets (1). Up to 80 % of DGF-3, DGF-2 and DGL-2 were released within 4 min, and this was followed by a gradual increment in the release rates up to 30 min. Diazepam release from batches DGL-3 and DGL-4 were significantly lower ($p < 0.05$) than the release from DGF and DGL-2 tablets (2 – 10 min). During this period, less than 80 % of diazepam was released (1). The difference in the release properties of diazepam noticed could be attributed to the difference in the mechanical strengths of tablets formed from both MCC-GossF and MCC-GossL. The DGL tablets were mechanically stronger than DGF tablets. Amongst the DGF tablets, DGF-4 had the least hardness which depicts its weak mechanical strength. All the batches had their

diazepam content maximally released within 30 min. The diazepam dissolution behavior of DGF and DAV tablets is shown (3). Diazepam from DGF formulations were significantly better released ($p < 0.05$) than from DAV formulations. The order of release was DGF-4 > DGF-3 > DGF-2.

This order was consistent at all the sampling times within 30 min. Amongst the DAV batches of tablets, DAV-3 and DAV-4 had better release within 10 min than DAV-2, after which the order of diazepam release was DAV-4 > DAV-3 > DAV-2. All the batches had their diazepam content maximally released within 30 min (2).



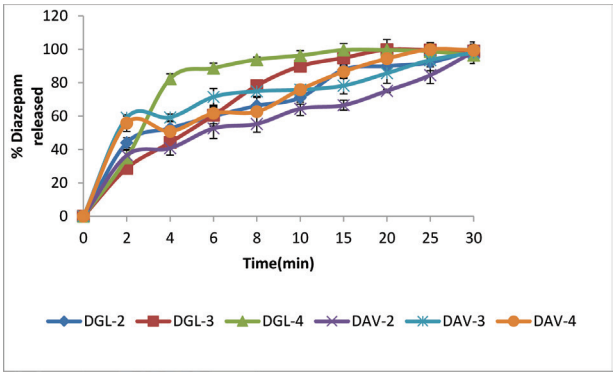
(1)



(2)

The dissolution profile of diazepam from DGL and DAV tablets is shown in Fig.3. Diazepam release from batch DGL-4 tablets from 4 – 30 min was consistently higher than from the other batches of tablets. This was followed by DAV-3 tablets up to 8 min. From 8 min upwards to 30 min, DGL-3 released the drug faster from the tablet than other batches except batch DGL-4. Other batches had comparable release behavior, although DAV-2 had the least release behavior from 4 min upwards.

Generally, all the batches of diazepam tablets passed the dissolution test as more than 80 % of their diazepam content was released within 30 min (BP, 2012; USP, 2009).



(3)

3.6. Kinetics and Mechanism of Diazepam Release

The kinetics and mechanism of diazepam release from the DGF, DGL and DAV tablets are shown in Table 5. The correlations (R^2) from the different models (Zero order, First order and Higuchi square root kinetics) were used to determine the kinetics while Korsmeyer – Peppas model was used to determine the mechanism of release. Korsmeyer – Peppas model classifies mechanism of drug release as Fickian (diffusion controlled) if $n \leq 0.5$, non Fickian if $n > 0.5$ but < 1.0, Case II if $n = 1.0$, Super Case II if $n > 1.0$ (Korsmeyer & Peppas 1981; Peppas, 1985). A mixed kinetics of release was observed. DGF-4 tablets followed Zero order, DGF-3 followed First order, while the rest of the formulations followed Higuchi (Table 5). The mechanism of drug release for all the batches was Fickian.

Table 5: Kinetics and mechanism of diazepam release.

Batch/ Model	Zero order kinetic	First order kinetic	Higuchi square root kinetic	Korsmeyer-Peppas	
	R^2	R^2	R^2	R^2	n
DGF-2	0.3999	0.1476	0.5168	0.6453	0.2128
DGF-3	0.3698	0.7624	0.5480	0.6744	0.1550
DGF-4	0.3063	0.1476	0.2750	0.4449	0.1257
DGL-2	0.7447	0.8387	0.9769	0.9861	0.3115
DGL-3	0.6895	0.7817	0.8218	0.8864	0.4628
DGL-4	0.4184	0.4647	0.4888	0.6174	0.2966
DAV-2	0.8343	0.7596	0.9699	0.9690	0.3581
DAV-3	0.6006	0.8970	0.9572	0.9129	0.1881
DAV-4	0.7311	0.8272	0.9653	0.9541	0.2839

Conclusion

The micromeritic indices of the powder mixes showed that DGF and DAV batches of powders had better flow properties than the DGL powders. Generally, it was observed that reduction in the flow behavior occurred as the quantity of diazepam contained in the powder mix increased.

All the powders showed evidence of densification and compressibility with the DGL powders showing the greatest reduction in volume upon agitation or tapping. All the test parameters for evaluation of flow ability showed that DGF powder blends flowed better than DGL powder blends. Tablets produced from these powder blends were intact without any physical defects. They also complied with British Pharmacopoeia set limits for uniformity of weight test, hardness and disintegration. The hardness of DGL tablets were significantly stronger ($p < 0.05$) than those of DGF tablets. Similarly, the friability of the different batches of the tablets complied with both the British Pharmacopoeia and United States Pharmacopoeia set limit for uncoated tablets except for batch DGF-4. Both DGL and DAV batches of tablets had a dilution potential up to 40 % while DGF had up to 30 %. This result conforms with their H-FR values. The assay of the tablets showed that the tablets maintained their label claim. Diazepam release from the tablets shows that all the tablets met with the USP specification for dissolution with DGF tablets having a faster release than DGL and DAV tablets. The kinetics of diazepam release from the tablets containing the different MCCs was mixed while the mechanism was Fickian. Diazepam tablets formulated with MCC-GossL and AVH-102 had better mechanical properties than those formulated with MCC-GossF. However, the MCCs obtained from *G. herbaceum* served as good dry binders in the formulation of diazepam tablets.

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Authors Contribution

Ofoefule, S.I. designed and supervised the work. Nwachukwu, N. anchored the bench work, collected and analyzed the data, conducted the literature search. Both authors wrote and corrected the manuscript.

Conflict of Interest

There is no conflict of interest. The research was fully sponsored by the authors.

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