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Investigation of the direct compression properties of microcrystalline starch (MCS) as a filler/binder/disintegrant in metronidazole tablet formulation

Y. E. Apeji*, Avosuahi Oyi, H. Musa, A. K. Olowosulu

Department of Pharmaceutics & Pharmaceutical Microbiology, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria

Abstract: This study investigates the incorporation of microcrystalline starch (MCS) as a filler/binder/disintegrant in metronidazole tablet formulation by direct compression. MCS was derived from cassava starch by partial enzymatic hydrolysis using α-amylase enzyme. Cassava starch obtained from the freshly harvested tubers of *Manihot esculenta* Crantz was subjected to enzymatic hydrolysis in a thermostatic water bath set to a temperature of 56ºC. The reaction was allowed to proceed for 5h at a pH of 6. Hydrolysis was terminated after 5h by lowering the pH to 3 with 0.1N HCl. It was then brought to a neutral pH 7 by the addition of 0.1N NaOH and the resulting MCS separated from the reaction mixture by centrifugation at 2800 rpm for 10 min. The MCS obtained was re-dispersed in ethanol to dehydrate it and spread out on a tray to dry at room temperature. Powder and compact characterisation of MCS was done in comparison to microcrystalline cellulose (MCC). Powder properties revealed more differences than similarities between both materials. Both materials had an angle of repose greater than 40º. Hausner's ratio and Carr's index were lower for MCS compared to MCC. Compaction behaviour analysed by Heckel and Kawakita equations reveals that both materials consolidate principally by plastic deformation. Tableting properties revealed that MCS has a better drug-release profile in terms of disintegration and dissolution parameters compared to MCC. This study confirms the suitability of MCS as a filler/binder/disintegrant for poorly compressible drugs.

Keywords: Microcrystalline cellulose, powder properties, compaction properties, enzymatic hydrolysis, Heckel equation and Kawakita equation.

INTRODUCTION

A large percentage of the drugs available for therapy of diseased conditions are formulated as tablets. They are the most frequently used dosage form because of their relative safety and ease of administration, amenable to large scale production, excellent stability profile and easy packaging, storage and transportation[1]. They are usually produced by the compaction of powders or granules[1] consisting mainly of the active pharmaceutical ingredient (API) and excipients. The excipients principally are responsible for tablet properties with respect to robustness, manufacturing feasibility, stability, safety and bioavailability. Excipients incorporated into any formulation are carefully selected in order to achieve the goal of the dosage form design. It therefore becomes imperative to study the material properties of these excipients because they play a major role in dosage form design.

In this study, MCS, a starch derivative obtained by partial hydrolysis using an enzyme (α-amylase) was investigated as a multifunctional excipient in the formulation of metronidazole tablets by direct compression. Several studies have been conducted by many workers on modified starches as excipients in the formulation of tablets. It was observed by many researchers that modification of starch improved its functional properties making it suitable for its target purpose in the dosage form. Modification was usually done in order to suit its purpose for its design.

The tablets for this study will be formulated by direct compression. The ease of manufacture favours direct compression but it presents some limitations. Powder mixtures for direct compression require sufficient plastic

***Corresponding author:**
Email: yonniapeji@yahoo.com.

deformation, good flow properties and a reasonable dilution capacity. These properties will be investigated in this study. The models of Heckel and Kawakita equations will be employed to evaluate the compressibility of the material which is an indirect measure of a material's ability to form tablets[2]. Tablet properties will be evaluated in comparison to tablets formulated with microcrystalline cellulose (MCC), a well known direct compression excipient. This study aims at minimising the number of excipients included in a formulation to reduce the risk of incompatibilities and lower considerably the overall cost of production of the final product.

MATERIALS AND METHODS

MATERIALS

The materials used for this study were all of pharmaceutical grade. They are all mentioned below;

A7595 α-amylase, Hydrochloric acid (Sigma-Aldrich laborchemikalien GmbH Germany), Stearic acid, Talc, Xylene, Ethanol, Metronidazole (BDH Chemicals Ltd Poole, England), MCC PH 101 (ATOZ Pharmaceuticals Ltd, Ambaltur, India), Sodium Hydroxide (Avondale Laboratories Ltd Banbury, England). Cassava Starch was extracted and processed in the Process Laboratory of the Department of Pharmaceutics & Pharmaceutical Microbiology, Ahmadu Bello University, Zaria.

METHODS

Production of microcrystalline starch (mcs)

Cassava starch was extracted from the freshly harvested tubers of *Manihot esculenta* Crantz using a method described elsewhere[3]. The method of Buwalda and Arends-Scholte[4] was adopted to prepare microcrystalline starch.

Slurry containing 40%$^{w}/_{w}$ of cassava starch was prepared in a beaker. The beaker containing the slurry was placed in a digital thermostatic water bath (Mcdonald Scientific International, Lagos, Nigeria) set to 56ºC. The pH of the slurry was adjusted to 6 using 0.1N HCl and 0.2%$^{v}/_{g}$ of α-amylase (BAN 240L) was introduced into the slurry. The reaction was allowed to proceed for five hours with intermittent stirring. The reaction was then terminated after 5h by lowering the pH to 2.5 with 0.1N HCl and subsequently neutralized by raising the pH to 7 with 0.1N NaOH. The reaction mixture was allowed to settle and the supernatant decanted. It was then washed several times with distilled water, centrifuged at 2800 rpm for 10 min before re-dispersing in ethanol (95%$^{v}/_{v}$) to dehydrate the microcrystalline starch (MCS) formed. The MCS was recovered by decanting the supernatant and air-dried.

Powder properties

The angle of repose was determined using a method described by Alebiowu[5] and calculated using the equation given below:

$$\theta = Tan^{-1}\, {}^{H}/_{R} \ldots\ldots\ldots\ldots\ldots Eqn.1$$

The flow rate was also determined using an Erweka flow apparatus (Type GDT, Erweka – Apparatebau - G.m.b.H Heusenstamm, West Germany).The time taken for the powder to flow through the orifice was noted and the flow rate was determined using the equation given below:

$$Flow\ Rate = \frac{Weight\ of\ Powder\ in\ grams}{Time\ of\ flow\ in\ seconds} \ldots\ldots\ldots\ldots Eqn.2$$

The particle density was determined using the liquid displacement method described by Odeku et al[6]. Bulk and tapped densities were determined using 50 g of the powder and used to calculate the Hausner's ratio and Carr's index using the equations given below:

$$Carr's\ Index = \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density} \times 100\% \ldots\ldots\ldots\ldots Eqn.3$$

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density} \ldots\ldots\ldots\ldots Eqn.4$$

The swelling capacity of the powder was estimated by a method described by Iwuagwu and Onyekweli[7]. The method of Kornblum and Stoopak[8] was used to determine the hydration capacity.

Two grams of each material was weighed and evenly distributed over the surface of a 70 mm tarred Petri-dish. The samples were placed in a dessicator containing distilled water in its reservoir (Relative Humidity=100%) at room temperature and the weight gained by the exposed samples at the end of the five day period was recorded and the amount sorbed was calculated from the weight difference as the moisture sorption capacity.

Dilution capacity

The drug and excipient were mixed in the following ratios: 10:90, 20:80, 30:70, 40:60, 50:50, 60:40, 70:30, 80:20, and 90:10. It was then compressed at varying compression loads on the Single Punch Tableting Machine (Type EKO, Erweka – Apparatebau - G.m.b.H Heusenstamm, West Germany). The crushing strength and tensile strength (Ts) of each binary mix was determined and recorded.

Compaction studies

Compacts of each material were prepared by weighing 500 mg individually and compressing at various compression loads ranging from 28.3-141.6 MN/m^2 on a Carver hydraulic hand press (Model C, Carver Inc., Menomonee

Falls, W.I). The dwell time was 30 s for each compression. Prior to compression, the 10.5 mm die and flat-faced punches were lubricated with 2%$^{w}/_{v}$ dispersion of magnesium stearate in ether–ethanol (1:1) solution. After ejection, the compacts were stored in a dessicator over silica gel for 24h to allow for elastic recovery and hardening. Their weights (W) and dimensions (thickness & diameter) were then determined to within ± 1 mg and 0.01 mm respectively and their relative densities (D) were calculated using the below equation:

$$D = \frac{W}{Vt \times \rho s} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Eqn.5$$

where V_t is the volume (cm^3) of the tablet and ρs is the particle density (g/cm^3) of the solid material. Heckel plots of ln (1/1-D) versus applied pressure (P) and Kawakita plots of P/C versus P were constructed for both materials.

Tablet formulation

Two batches of tablets were prepared by direct compression with metronidazole as the model drug. A batch size of 100 tablets was prepared. The tablet formula for each batch is given in Table 1.

The tablets were formulated by mixing the active drug and the filler/binder/disintegrant in a mortar using a pestle to achieve a uniform blend. The calculated quantities of the lubricant and glidant were weighed on an electronic scale and incorporated into the powder mix. Mixing continued for another 5 min and tablets were compressed using a single punch tableting machine (Type EKO, Erweka – Apparatebau – G.m.b.H Heusenstamm, West Germany) fitted with 12 mm concave – faced punches. The tablet weight was 500 mg.

Evaluation of tablet properties

Twenty tablets from each batch were selected at random and weighed individually using an electronic balance (Mettler Analytical Balance, Philip Harris Ltd., England). Their mean weights and standard deviations were determined based on an official method[9].

Tablet thickness and diameter was measured using a screw guage micrometer. A mean of five determinations was obtained and recorded.

Ten tablets randomly selected from each batch were crushed using a Monsanto hardness tester. Pressure was applied by turning the knob until the required pressure that crushed the tablet was read in terms of kilogram force (kgf) on the scale. The mean of ten determinations on each batch was recorded.

The load *P*, needed to fracture the tablets (n=10) was determined. Tablet tensile strength (*TS*) values were calculated from the equation:

$$TS = \frac{2P}{\pi dt} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{Eqn.6}$$

Where *TS* is the tensile strength

P is the load required to crush the tablet,

t is the thickness and

d is the diameter of the tablet.

Ten tablets were selected at random from each batch, dusted and weighed together using the electronic balance and then allowed to tumble in an Erweka friabilator set at 25 rpm for 4 min and then stopped. The tablets were dusted again and reweighed. The percentage loss in weight was calculated for each batch of tablets.

The disintegration time for each batch of tablets was determined in distilled water at 37 ± 0.5°C using the Erweka disintegration test apparatus (Type ZT3, Erweka – Apparatebau - G.m.b.H Heusenstamm, West Germany). Six tablets were tested and the time taken for each tablet to break into small particles and pass through the mesh was recorded as the disintegration time.

Before dissolution studies, the following was carried out;

A 0.1 mg/ml stock solution of metronidazole was prepared by dissolving 100 mg of metronidazole in 1000 ml of 0.1N HCl. Serial dilution was performed to prepare solutions of varying concentrations ranging from 0.3125–10 µg/ml. The

Table 1. Tablet formula for Metronidazole Tablets

Ingredients	Batch	
	I	II
Active drug (40%)	MET (200)	MET (200)
Filler/binder/disintegrants (59%)	MCS (295)	MCC (295)
Lubricant (0.5%)	Stearic acid (2.5)	Stearic acid (2.5)
Glidant (0.5%)	Talc (2.5)	Talc (2.5)
Total (mg)	500	500

Metronidazole- MET, Microcrystalline cellulose-MCC & Microcrystalline starch-MCS

absorbance of each concentration was taken at 277 nm and plotted against the various concentrations to obtain the calibration curve for metronidazole. The linear regression equation (y = 0.04x + 0.13) for the graph was resolved from the plot and used to calculate the amount of drug released with time during dissolution studies.

The dissolution rate of the tablets was determined using an Erweka dissolution apparatus. The dissolution medium was 1000 ml of 0. 1N HCl maintained at 37 ± 0.5°C. The revolution of the basket containing the test tablet was 100 rpm. Ten millilitres of the sample was withdrawn from a position half way between the surface of the dissolution medium and the top of the rotating basket at 5 min intervals for 1h. Each volume of sample withdrawn was replaced with an equivalent volume of dissolution medium maintained at the same temperature. A ten fold (1:9) dilution with the dissolution medium was done for each sample withdrawn before absorbances of the samples were read at 277 nm[9] using a UV/VIS Spectrophotometer (Helios Zeta UV–VIS Spectrophotometer, Thermo Fischer Scientific Inc., Cambridge, UK). The percentage drug released was plotted against time to generate a dissolution curve.

Statistical analysis

Statistical analysis was carried out to compare the tableting properties of MCS with MCC in the formulation of metronidazole tablets using the student's t-test as a statistical tool. At 95% confidence interval, $p \leq 0.05$ were considered significant.

RESULTS AND DISCUSSION

Materials employed as directly compressible excipients are usually evaluated in powder as well as compact form. The powder parameters include moisture content, particle size, particle density, bulk and tapped densities, Hausner's ratio, Carr's index, angle of repose etc. The compact parameters are compact dimensions, hardness, Heckel and Kawakita analysis[10-12].

Results on the physicochemical properties of MCS and MCC are presented in Table 2. Angle of repose for both materials exceeded 40° indicating that these materials were poor flowing. This result was consistent with the poor flow rates observed for both materials. This could be attributed to the particle size of the materials. Materials having small particle sizes equivalent to powders corresponds to poor flowability due to increased interparticulate friction between particles. Bulk density is primarily dependent on particle size, size distribution and particle shape. This parameter is an indirect measure of flow and usually determines the die fill volume. Materials having higher bulk density require lower die fill volume than those having small bulk density. The values recorded for bulk and tapped densities for both materials are presented in Table 2 and were used to compute Hausner's ratio and Carr's index for both materials. Again, the values recorded for Hausner's ratio and Carr's index (Table 2) exceeded the requirements for good flowability confirming the poor flowability of both materials. Hausner's ratio greater than 1.25 and Carr's index exceeding 20% is an indication of poor flow. Results for swelling power, hydration capacity and moisture sorption capacity are also presented in Table 2. Generally, the intrinsic properties of

Table 2. Physicochemical Properties of MCS and MCC

Parameter	MCS	MCC
Angle of repose (°)	45.4±1.03	41.5±1.77
Flow rate (g/s)	1.5±0.08	0.7±0.02
Bulk density (g/cm^3)	0.61±0.02	0.39±0.02
Tapped density (g/cm^3)	0.79±0.02	0.55±0.01
Hausner's ratio	1.30	1.41
Carr's Index	23	29
Particle density (g/cm^3)	1.38	1.48
Swelling power	1.50	1.31
Hydration capacity	0.82	0.84
Moisture sorption capacity (%)	19	10

Table 3. Dilution Potential for MCS and MCC

Material	Proportion of drug
	MET
MCS	40:60
MCC	60:40

swelling power, hydration and moisture sorption capacities have been recognized as providing qualitative assessments of potential disintegrating agents[13].

The carrying capacity (Dilution potential) for MCS and MCC was investigated and the observations recorded in Table 3. The results show that MCC possesses a greater dilution capacity compared to MCS. This confirms the superiority of MCC as a direct compression excipient attributed to its low bulk density conferring on it a high capacity to accommodate a large percentage of a poorly compressible drug and still retain its compressibility. It possesses high covering power[14].

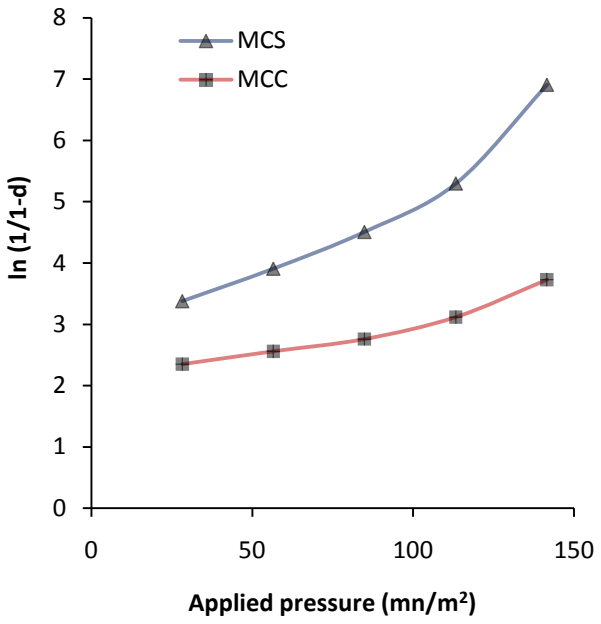

Fig 1. ln (1/1-d) against applied pressure for MCS and MCC compacts

Figure 1 show the Heckel plots for MCS and MCC and the parameters derived from Heckel and Kawakita plots are presented in Table 4. A linear fit which included much data from the compression part of the plot was obtained for MCS and MCC indicating that both materials consolidate mainly by plastic deformation. The slope of the Heckel plot was calculated from the compression part of the plot and this parameter (slope) provides information on the total deformation of the powder during the compression phase. A lower Heckel slope corresponds to a higher mean yield pressure and thus a higher resistance against deformation while a higher Heckel slope corresponds to a low mean yield pressure and thus a higher and easier deformation [15]. The mean yield pressure (P_Y) is defined as the pressure at which plastic deformation of a particle is initiated[16].

The results show that MCS has a low P_Y (Yield Pressure) compared to MCC and so readily deforms on compression at low pressures. The D_0 value refers to the relative density at zero pressure and it was found to be higher with MCS in comparison to MCC. The total deformation occurring in the powder was reflected by a higher value of D_A for MCS compared to MCC. D_B values are an indication of the fragmentation tendency of a material and it was higher for MCC than MCS indicating that MCC does not deform exclusively by plastic deformation but also by brittle fracture. Khan and Rhodes[17] observed that an increase in compression pressure caused some fragmentation in MCC. High D_B values are caused by fragmentation while low D_B values are typically connected to plastically deforming materials[18, 19].

A representative Kawakita plot for the two materials is displayed as Figure 2. A linear relationship was obtained at all compression pressures used with a correlation

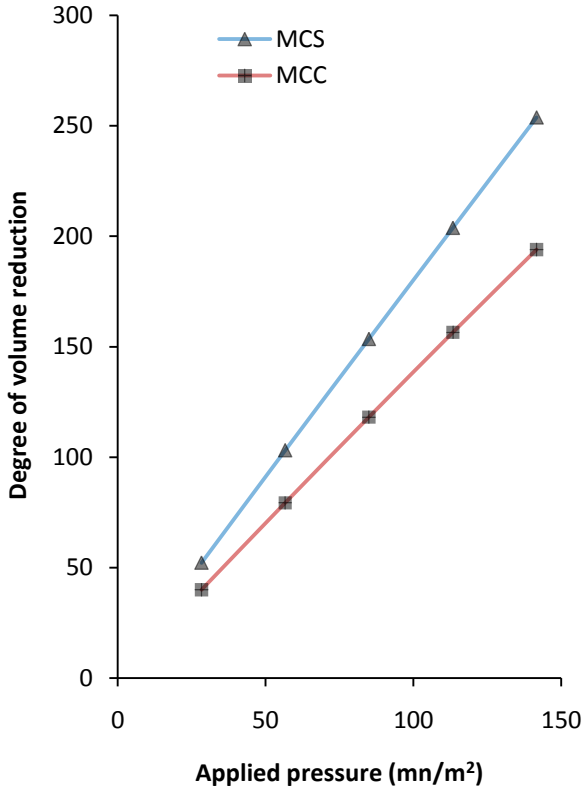

Fig 2. Degree of volume reduction against applied pressure (Kawakita plots for MCS and MCC)

coefficient (r^2 = 0.999) for both materials. The Kawakita parameters were resolved from the slope and intercept of the plot. The D_I value is a measure of the packed initial

Table 4: Parameters from Heckel and Kawakita Plots

Material	Heckel Plot				Kawakita Plot			
	P_Y	D_0	D_A	D_B	a	B	D_I	P_K
MCS	45.45	0.413	0.933	0.520	0.562	0.809	0.438	1.24
MCC	111.11	0.264	0.874	0.610	0.735	0.673	0.265	1.49

relative density with the application of small pressures of tapping[20]. Values of D_I for MCS was higher than that of MCC confirming what was observed in Heckel analysis where MCS exhibits a greater degree of densification and closer packing than MCC (Table 4). The P_K value is an inverse measurement of the plastic deformation occurring during the compression process[20]. The lower the P_K value, the higher the total plastic deformation occurring during compression[20]. A higher degree of plastic deformation was observed with MCS compared to MCC (Table 4). Plastic deformation creates more contact points for interparticulate bonding resulting in tablets with sufficient mechanical strength[21, 22].

Evaluation of tablet properties revealed that the tablets from both batches met the BP, 2002 requirements for weight uniformity of tablets, not exceeding the limit of ± 5%.

The addition of a glidant to the formulation must have enhanced the flow of the formulation, ensuring that uniform volumes of the powder blend were fed into the die cavity resulting in tablets of uniform weight. The results of the diameter and thickness of tablets are also given in Table 5.

Table 5. Tablet Properties

Property	Batch I	Batch II
Uniformity of weight (mg)	505±13	500±11
Thickness (mm)	4.05±0.05	4.04±0.04
Diameter (mm)	12.06±0.05	12.08±0.01
Crushing strength (N)	94±0.5	92±1.2
Tensile strength (MN/m^2)	1.23±0.5	1.20±1.2
Friability ($\%^w/_w$)	0.78	0.4
Disintegration time (min)	20.5±1.59	>60
Dissolution efficiency (30 min) (%)	80	19
$T_{50\%}$ (min)	17	-
$T_{90\%}$ (min)	-	-

Data derived for the crushing strength and tensile strength are shown in Table 5. It is an index used to measure the hardness of a tablet. Although, there is no official limit for tablet hardness, values falling within the range of 40-70N are generally acceptable. Results obtained for batches of tablets containing MCS and MCC all exceeded the higher limit of 70N, giving rise to very hard tablets that may not disintegrate within the shortest possible time.

Tablet friability is a measure of the weakness of the tablets. Generally, a limit not exceeding 1% is acceptable. The friability values for all the batches ranged from 0.4 - 0.78% with MCC tablets giving much lower values in comparison to MCS tablets. This agrees with the findings of Bastos et al[23] that tablets formulated with microcrystalline cellulose presented a lower friability and high hardness. All batches containing MCS and MCC passed the friability test.

The drug-release profile of tablets was investigated by carrying out tests on disintegration and dissolution for all the batches. The results are presented in Table 5. The disintegration time for batches containing MCS and MCC ranged from 20.5 to > 60 min with those batches of tablets formulated with MCS giving shorter disintegration times compared to tablets formulated with MCC whose tablets did not disintegrate after 60 min of the procedure. None of the batches disintegrated in less than 15 min. These results could be attributed to the predetermined hardness of the tablets which was quite high for both batches (>70N).

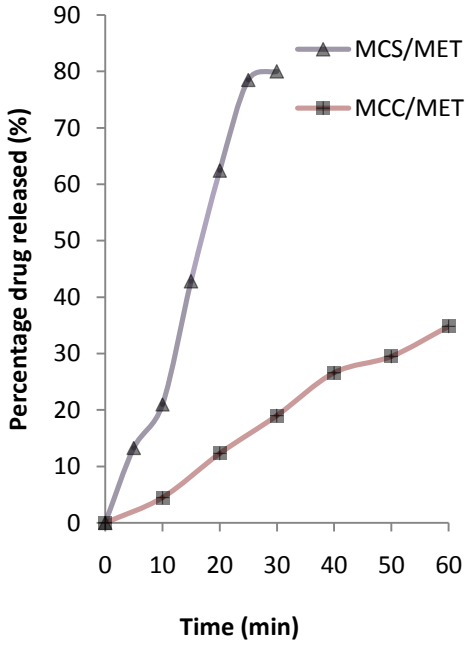

Fig 3. Percentage drug released against time for MCS/MET and MCC/MET tablets

The dissolution profiles of the tablets are shown in Figure 3. The dissolution efficiency (D.E).i.e. percentage of drug released after 30 min ranged from 19-80% with MCS tablets releasing a greater percentage of the drug after 30 min in comparison to MCC tablets.

It can be seen from the results that the dissolution corresponds to the disintegration time. Faster tablet disintegration resulted in a faster drug release. Batches formulated with MCS had a better dissolution profile compared to MCC. Differences in crushing strength, disintegration time and dissolution profile for both batches of tablets were statistically significant at $p \leq 0.05$.

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