

Research Article**EVALUATION OF A NEW TABLET DISINTEGRANT FROM DRIED PODS OF ABELMUSCUS ESCULENTUS L (OKRA)**

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ABSTRACT

The disintegrant property of dried pods of Okra was investigated in metronidazole tablet formulations using physicochemical properties of relevance to tableting, disintegration times and dissolution rates as assessment parameters. X-ray fluorescence spectrometric analysis of the elemental constituents of the pods was determined and the comparative effects of the Okra powder and two standard disintegrants – corn starch B.P and microcrystalline cellulose—on crushing strength, friability, disintegration time (D) and dissolution characteristics of metronidazole tablet formulation made by direct compression method were studied. Okra powder contained potassium, sodium and calcium while heavy metals like lead and mercury were absent. Okra powder exhibited good flow and had superior hydration ($p < 0.05$) and moisture sorption ($p < 0.01$) capacities compared to corn starch B.P and microcrystalline cellulose. Ranking for the values of the crushing strength – friability ratio for the tablet formulation was corn starch B.P > microcrystalline cellulose > Okra powder. Tablets formulated with Okra powder passed the official disintegration test. Okra powder produced a more significant reduction in the disintegration time of formulated metronidazole tablets than microcrystalline cellulose but less than corn starch. Tablets containing Okra powder showed good dissolution profile with T_{50} and T_{90} values comparable to those of corn starch B.P and microcrystalline cellulose. The result shows the potentials of Okra powder as tablet disintegrant and suggests that it could be further developed for commercial purposes.

KEYWORDS Okra, Cornstarch B.P, Microcrystalline cellulose, Metronidazole tablet, Disintegrant properties.

INTRODUCTION

The International Pharmaceutical Excipients Council (IPEC) has defined pharmaceutical excipients as substances other than the active drug or prodrug which have been appropriately evaluated for safety and are included in a drug delivery system to either aid in the processing of system during its manufacture; or protect, support or enhance stability, bioavailability, or patient acceptability; assist in product identification; or enhance any other attribute of the overall safety and effectiveness of the drug during storage or use¹. The role of excipients in determining the quality of a formulation and in many cases the bioavailability of a drug from tablets has received considerable attention in recent years and disintegrants play a significant role in this regard. Disintegration exposes a greater surface area of tablets to the dissolution medium; hence it plays an important role in a

tablet's dissolution before the active drug substance is finally released from the tablet's structure into the body. Since a tablet is not useful until its active component is made available for absorption, the disintegrant is arguably the most important excipient in a tablet. A tablet disintegrant is that excipient which facilitates the break up of the tablet in a liquid environment into fine particles prior to dissolution of the active drug and its absorption from the gastrointestinal tract. Several mechanisms have been proposed to rationalize the action of disintegrant and these include porosity and capillary action, rate of water uptake into the tablet, swelling of disintegrant particles, gas release, melting and enzymatic action, heat of wetting and lysis of physico-chemical bonds^{2, 3}. There is constant pressure to search for new excipients to attain the desired set of functionalities. Improved functionality of excipients can be obtained by developing new excipients, new grades

of existing materials, and new combinations of existing material. ⁴

Okra is an annual or perennial herbaceous plant, growing up to 2m tall straight up with very little phototropism. The pod

Xylene (Hopkin and Williams, London). The Okra pods were obtained from local farmers in Ibadan, Nigeria and authenticated. Water was double distilled and every other chemical was of analytical

Table 1: Powder properties of Okra powders corn starch and Microcrystalline cellulose.

Materials	Moisture Content (%)	Moisture Sorption capacity (%)	Swelling capacity	Hydration capacity	Hausner's ratio	Carr's index	Particle density (gcm ⁻³)
FOP-OV	10.9	47.0	6.40	7.02	1.32	24.4	2.02
OST-OV	11.0	45.0	3.75	4.91	1.35	26.0	2.12
TOP-OV	12.1	47.5	4.45	7.06	1.35	25.8	1.95
FOP-SD	12.8	52.0	7.92	11.08	1.21	16.9	1.39
CS	6.22	18.0	0.72	1.83	1.31	23.8	1.37
MCC	7.20	18.2	1.63	2.20	1.53	34.9	1.42

FOP-SD: Fresh Okra pod dried in the sun; FOP-OV: Fresh Okra pod dried in the oven-dried ; TOP-OV: Over-ripened Okra pod dried in the oven ; OST-OV: Okra pod stalk dried in the oven; MCC: Microcrystalline cellulose; CS: Corn starch

could be green, red or purple, long, slender or chunky with numerous ridges running along the length of the pod. The pod varies in length from a few to about 7 cm in length and 1-4 cm in width. Okra plant grows very fast; therefore, it must be harvested every two days. The crop can be grown on all soil types, although sandy loam soils high in organic matter are the most desirable. Okra is among the most heat-and drought-tolerant vegetables in the world; once established, it can survive severe drought conditions. The edible pods are used in soups and as a vegetable ⁵. In the present study, the disintegrant ability of dried powdered pods of *Abelmoschus esculentus* (L) Moench (Okra) was evaluated with a view to providing information on its potential usefulness in tablet formulation and production.

MATERIALS AND METHODS

The materials used were: metronidazole BP, corn starch BP, polyvinylpyrrolidone, PVP (30,000, Merck, Germany), lactose (DMV Veghel, Netherlands) and microcrystalline cellulose (BDH Chemical, Poole, U.K),

grades.

Preparation of Okra pod powders

A 5.0 kg weight of fresh Okra pods from which the stalk and the apex of the pod had been removed was weighed, sliced with a hand knife and spread in the sun for 72 hours. The sun drying was done between 9:00 hrs and 16:00 hrs daily. The average temperature during this period was 33⁰C and the relative humidity was 67%. The sun dried pods were then crushed into tiny bits in a mortar and then pulverized in an osterizer blender to produce powdered Okra labeled as FOP-SD. Fresh Okra pods without the apex and the stalk, overripened pods (pods that have become tough and fibrous due to delay in harvesting) without the apex and the stalk, the stalk and the apex were prepared as above but dried in a Gallenkamp oven (Model BS, UK) at 60 °C for 9 hours to produce powdered Okra labeled as FOP-OV, TOP-OV and OST-OV respectively

Evaluation of physicochemical properties of Okra powders

The hydration capacity, swelling index and moisture sorption capacity were determined using established procedures⁶⁻⁸.

Elemental constituents of the Okra powder were determined on the Link Analytical XR300 (Wallis Worthing, Europe). The particle density was determined by the pycnometer method using the liquid immersion technique with benzene as the displacement fluid. The bulk density of each powder at zero pressure (loose density) was determined by pouring the powder at an angle of 45° through a funnel into a glass measuring cylinder with a diameter of 21 mm and a volume of 50 mL⁹. Determinations were made in triplicate. The relative density, D₀, of each powder was obtained from the ratio of its loose density to the tapped density. Tap density was determined by subjecting the powder in a graduated cylinder to 300 taps by a standardized tapping procedure of 38 taps per minute¹⁰. The Hausner's ratio was determined as the ratio of the initial bulk volume to the tapped volume. The Carr's index was calculated using bulk and tapped densities data in Equation 1

$$\text{Carr's Index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100 \% \quad \text{Eq.1}$$

Preparation of tablets

Batches (500 mg) of metronidazole formulations containing 50 % w/w metronidazole powder, 2.5 % - 15 % disintegrant, 5 % PVP (binder) and lactose diluent were compressed for 30s into tablets on a hydraulic hand press (Model C, Carver Inc., Menomonee Falls, WJ, USA) using a 12.5 mm die and flat faced punches lubricated with a 2%w/v dispersion of magnesium stearate in 96 % ethanol. The tablets were stored over silica gel for 24 hr to allow for elastic recovery and hardening, and prevent false low yield values. Tablet weights and dimensions were determined within ±1mg and 0.01mm respectively, and their relative densities (D) were calculated.⁸

Determination of tablet properties

The crushing strength of the tablets was determined at room temperature by diametric compression¹¹ using a Monsanto Hardness tester. The percentage friability of the tablets was determined using the Veego tablet friability apparatus (Veego Scientific Devices, Mumbai, India) operated at 25 rpm for 4 min. The disintegration times of the tablets were determined in distilled water at 37 ± 0.5 °C using BP Manesty disintegration test unit (Manesty Machines, Poole, U.K.). The rate of dissolution of metronidazole from the tablets was studied in a rotating basket BP Apparatus II [Veego digital dissolution tester, India] operated at 100 rpm using 900 mL of 0.1 M hydrochloric acid maintained at 37± 0.5 °C and the amount of metronidazole was determined using a UV spectrophotometer (Pye Unicam, Middlesex, England) at the wavelength 250nm

RESULTS AND DISCUSSION

The British Pharmacopoeia¹² gives limit tests for a number of possible contaminants in pharmaceutical raw materials which may be introduced into the finished product during processing. Such tests include those for lead, arsenic, calcium, iron, potassium, aluminium, halogens and a host of others. Although the Pharmacopoeial requirements are not categorical on the exact tolerable level of any possible contaminant, it should not be presumed that unusual impurities are tolerated. X-ray fluorimetric (XRF) analysis of the Okra powder showed the presence of chromium, cobalt, bromium and nickel in trace amounts ; and sodium , potassium and zinc in levels comparable with those of the official corn starch B.P. Heavy metals like lead and mercury were however absent. The presence of heavy metals in formulated products is highly undesirable as they form stable covalent or co-ordinate complexes with body protein and can also act as catalyst (due to their variable valency state) to induce auto-oxidative reactions. The Pharmacopoeia

has therefore placed stringent limits on the amount of lead and other heavy metals that may be present in pharmaceutical products
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Swelling, which is generally accepted as an indication of tablet disintegration ability can be assessed by the determination of hydration capacity, swelling capacity and moisture sorption profile¹⁴. The hydration capacity values obtained for the Okra powders were greater than those of microcrystalline cellulose and corn starch (Table 1). OST-OV with the lowest hydration capacity of 4.91 is capable of absorbing about five times its own weight of water ; and approximately thrice more water than corn starch and about twice more water than microcrystalline cellulose. The swelling capacity values of Okra powders which reflect the increase in volume of Okra powders following water absorption are greater than the values for corn starch and microcrystalline cellulose. Thus, if Okra powder was incorporated in tablet formulation as a disintegrant it would probably produce tablet disintegration by two mechanisms: capillary or wicking due to inter-particulate water and swelling. In addition, the relatively higher hydration and swelling capacity values observed for the Okra powders compared to corn starch, and microcrystalline cellulose could possibly be due to the higher powder porosity of the Okra powders (Table 1).The superior hydration and swelling capacities of the Okra powders ($P < 0.05$) would suggest that they may likely be better disintegrant than corn starch and microcrystalline cellulose. The absorption of moisture by solid dosage forms and excipients provide information for selecting excipients and for determining the humidity control required during production and storage. The amount of moisture absorbed by drugs and excipients affects the flow, compression characteristics and hardness of tablets. Water interacts with pharmaceutical solids at virtually all stages of manufacture. Therefore, water – powder interaction is a

major factor in the formulation, processing and performance of excipients and solid dosage forms. The moisture sorption capacity of the Okra pods were significantly ($P < 0.01$) higher than the values obtained for corn starch and microcrystalline cellulose. In addition, the moisture contents of the Okra powders were high. The formation of film of moisture on the Okra powder surface may reduce friction at the die wall by acting as an internal lubricant. The moisture decreases tablet adhesion to the die wall and allows easy tablet ejection. It also increases the ease with which the individual particles can slip and flow during compression. However, it is important that the moisture content be kept as low as possible during storage to prevent microbial spoilage, hydrolysis and enzymatic decomposition. Consequently, Okra powders would need to be dried further if it is to be used as an excipient in the formulation of hydrolysable drugs such as aspirin.

The flow properties of a powder are essential to determine its suitability as a direct compression excipient. Hausner ratio and Carr's index are considered as indirect measurement of powder flowability¹⁵. Powder flow phenomenon is complex and multi-dimensional depending on many powder characteristics and other factors¹⁶. Hausners ratios greater than 1.25 indicate poor flow; Carr's index below 16 % indicates good flowability while values above 35 % indicate cohesiveness. In this study, the values of Hausner ratio and Carr's Index showed that the Okra powders except FOP-SD have poor flow. However, a gliddant may be added to further improve flow when Okra powders are used in solid dosage production processes. The Hausner ratio previews the degree of densification which could occur during tableting. The higher the ratio, the greater the propensity of the powder to densify¹⁷. The result showed that Okra powders may densify more than corn starch but less than microcrystalline cellulose.

TABLE 2: VALUES OF CRUSHING STRENGTH(CS), FRIABILITY(F) AND CRUSHING STRENGTH- FRIABILITY RATIO (CS-FR) FOR METRONIDAZOLE TABLET FORMULATION

DISINTEGRANT	CONC (%w/w)	CRUSHING STRENGTH (N)	FRIABILITY (%)	CS-F
None	0.0	>150	0.21	714.28
FOP-OV	2.5	77.0	0.35	220.00
	5.0	57.3	0.42	136.43
	7.5	48.0	0.44	109.09
	1.0	38.7	0.52	74.42
	12.5	27.3	0.74	36.89
	15.0	22.7	0.95	23.90
FOP-SD	2.5	44.7	0.27	165.56
	5.0	38.0	0.81	46.91
	7.5	36.7	0.92	39.89
	10.0	26.0	0.96	27.08
	12.5	21.3	0.96	22.19
	15.0	18.0	1.33	13.53
OST-OV	2.5	93.3	0.34	274.41
	5.0	96.0	0.58	165.52
	7.5	67.3	0.68	98.97
	10.0	39.3	0.96	40.94
	12.5	34.0	1.11	30.63
	15.0	26.7	1.32	20.23
TOP-OV	2.5	101.0	0.63	160.32
	5.0	90.7	0.66	137.42
	7.5	84.0	0.68	123.53
	10.0	69.3	1.00	69.30
	12.5	58.0	1.02	56.86
	15.0	47.3	1.09	43.39
CS	2.5	129.0	0.34	379.41
	5.0	135.3	0.61	221.80
	7.5	126.7	0.66	191.97
	10.0	125.5	0.69	181.88
	12.5	114.7	0.88	130.34
	15.0	104.0	0.88	118.18
MCC	2.5	145.0	0.60	241.67
	5.0	142.0	0.63	225.40
	7.5	140.0	0.65	215.39
	10.0	138.0	0.67	205.97
	12.5	136.0	0.69	197.10
	15.0	136.0	1.43	95.11

of tablet strength and weakness, respectively. There are now requirements for it in the British Pharmacopoeia¹² but with no clear limits for acceptance or rejection of tablet batches probably because the desired CS is largely dependent on the intended use of the tablet while tablets that lose less than 1% of their weight during the friability test are generally considered acceptable. The mechanical strength of tablets can also be measured by the crushing strength – friability ratio (CSFR)¹⁸. Generally, the higher the CSFR, the stronger the tablet. Okra powders formed strong tablets. Metronidazole tablets formulated with corn starch and microcrystalline cellulose had higher CS-FR values than tablets formulated with Okra powders. This suggests that corn starch and microcrystalline cellulose formed stronger tablets than Okra powder.

Tablets containing Okra powders generally passed the official disintegration test for uncoated tablets i.e. <15 mins. At all concentrations, tablets formulated with Okra powders disintegrated faster than those formulated with microcrystalline cellulose but slower than tablet containing corn starch. This does not conform to the higher swelling capacity and water retention capacity observed for Okra powders over corn starch. This may probably be because Okra powder disintegrated by other mechanism such as porosity and capillary action in addition to the mechanism of swelling and development of disruptive forces within the compact. Moreover, hydration and swelling capacities are not absolute indices of disintegrant efficacy¹⁹. Table 2 shows that there was a general decrease in disintegration times of formulated metronidazole tablets as the concentration of Okra powder increases. Similar observations on relationship between concentration of disintegrants and disintegration times have been reported in previous studies with corn starch²⁰. Okra powder produced a more significant reduction ($p < 0.05$) in the disintegration

time of formulated metronidazole tablets than microcrystalline cellulose but less than corn starch. Metronidazole tablets containing 15% w/w of TOP-OV disintegrated within 3.2 minutes suggesting the possibility of its use in immediate release formulations. Tablets containing Okra powder showed good dissolution profile. Figure 1 shows representative plots of the dissolution profile of Okra powders. There was a general increase in dissolution rates as concentrations increases. Table 3 shows that metronidazole tablets containing 12.5% w/w TOP-OV had the lowest T_{50} (<3 minutes), even lower than T_{50} of tablets formulated with corn starch at same concentration and within 5 minutes, 100 % dissolution was achieved. This may imply a faster onset of action and as such may be useful in immediate release formulations. Tablets formulated with OST-OV also showed faster onset of action. There exist a fair linear correlation between T_{50} and disintegration time, D , for FOP-OV ($r = 0.875$, $P < 0.05$) and FOP-SD ($r = 0.858$, $p < 0.05$). A plot of $\ln(c_s/c_s - c)$ against the time in the Noyes-Whitney equation generally showed two linear portions corresponding to the phases of drug dissolution from the tablet surface and from the de-aggregated fine particles. Figure 2 shows representative plots of $\ln(c_s/c_s - c)$ against the time for Okra powders. The time at which the lines intersect, T_1 correspond to the point in time when the tablet disintegrated.

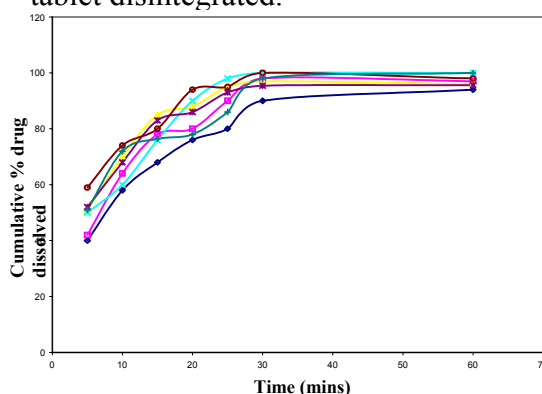


FIG 1. Dissolution Profile of Metronidazole Tablets Containing FOP-SD

◆,0%;■,2.5%;▲,5.0%;×,7.5%;×,10%;●,12.5%;+,15.0%

TABLE 2: Values of crushing strength, friability and crushing strength- friability ratio for Metronidazole tablet

Disintegrant	Conc (%w/w)	Crushing strength (n)	Friability (%)	Cs-F
None	0.0	>150	0.21	714.28
FOP-OV	2.5	77.0	0.35	220.00
	5.0	57.3	0.42	136.43
	7.5	48.0	0.44	109.09
	1.0	38.7	0.52	74.42
	12.5	27.3	0.74	36.89
	15.0	22.7	0.95	23.90
FOP-SD	2.5	44.7	0.27	165.56
	5.0	38.0	0.81	46.91
	7.5	36.7	0.92	39.89
	10.0	26.0	0.96	27.08
	12.5	21.3	0.96	22.19
	15.0	18.0	1.33	13.53
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	5.0	96.0	0.58	165.52
	7.5	67.3	0.68	98.97
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	12.5	34.0	1.11	30.63
	15.0	26.7	1.32	20.23
TOP-OV	2.5	101.0	0.63	160.32
	5.0	90.7	0.66	137.42
	7.5	84.0	0.68	123.53
	10.0	69.3	1.00	69.30
	12.5	58.0	1.02	56.86
	15.0	47.3	1.09	43.39
CS	2.5	129.0	0.34	379.41
	5.0	135.3	0.61	221.80
	7.5	126.7	0.66	191.97
	10.0	125.5	0.69	181.88
	12.5	114.7	0.88	130.34
	15.0	104.0	0.88	118.18
MCC	2.5	145.0	0.60	241.67
	5.0	142.0	0.63	225.40
	7.5	140.0	0.65	215.39
	10.0	138.0	0.67	205.97
	12.5	136.0	0.69	197.10
	15.0	136.0	1.43	95.11

TABLE 3: DISINTEGRATION AND DISSOLUTION CHARACTERISTICS OF METRONIDAZOLE TABLETS CONTAINING THE VARIOUS DISINTEGRANTS

DISINTEGRANT	CONC (%w/w)	D (min)	T ₅₀ (min)	T ₉₀ (min)	T ₁ (min)
None	0.00	18.92	8.2	30.5	25.5
	2.5	12.38	6.4	24.0	21.00
	5.0	11.17	5.0	21.3	20.50
	7.5	8.17	4.8	22.6	14.85
	10.0	6.46	4.2	19.8	14.60
	12.5	4.54	4.1	18.5	14.00
	15.0	6.42	4.9	25.3	15.00
FOP-SD	2.5	14.83	4.2	22.0	14.90
	5.5	11.70	3.8	19.5	14.85
	7.5	8.67	3.5	18.0	13.90
	10.0	7.55	3.2	13.7	9.70
	12.5	5.83	3.0	10.0	4.90
	15.0	5.25	6.2	61.5	19.80
OST-OV	2.5	14.48	6.0	17.0	15.3
	5.5	9.92	7.6	21.2	15.2
	7.5	8.17	8.5	20.2	15.1
	10.0	7.50	8.4	19.0	14.9
	12.5	6.78	7.8	19.0	14.8
	15.0	5.92	10.2	19.0	20.5
FOP-OV	2.5	15.0	4.0	25.20	19.9
	5.5	12.63	6.3	28.00	19.8
	7.5	7.58	5.3	14.60	19.5
	10.0	5.33	5.1	18.70	19.0
	12.5	4.17	2.3	4.80	15.1
	15.0	3.2	4.2	9.10	9.8
TOP-OV	2.5	3.33	3.9	19.0	19.8
	5.0	6.80	4.2	22.5	14.8
	7.5	6.30	4.2	18.6	14.8
	10.0	5.25	3.8	17.0	10.0
	12.5	5.65	3.4	13.0	9.9
	15.0	4.50	7.7	15.8	19.4
CS	2.5	15.2	5.3	18.0	19.0
	5.0	15.0	5.2	25.3	15.0
	7.5	14.6	5.1	25.1	14.9
	10.0	14.17	9.9	25.0	14.8
	12.5	14.08	5.0	18.8	14.8
	15.0	12.5	5.0	9.9	14.7
MCC					

The apparent lack of correlation between the disintegration time, T_1 estimated from the dissolution profile and D obtained from the disintegration test is attributable to the difference in agitation intensity in the two determinations. The rigorous stirring in the manesty disintegration test apparatus is not comparable with the streamlined flow that was operative in the dissolution-test apparatus. Hence, the manesty disintegration unit produced shorter disintegration time. All the tablets formulated with Okra powders passed the British Pharmacopoeia¹² specifications for disintegration time of uncoated tablets (<15 minutes) while the time required for 90 % drug release (T_{90}) was also within one hour which is characteristic of immediate release formulations Table 3. In addition, all the tablets passed the BP dissolution test for tablets which specifies that at least 70 % of the drug substance should be in solution after 30 minutes. The results show that Okra powder is potentially useful as a disintegrant and may be a suitable alternative to corn starch B.P and microcrystalline cellulose in tablet

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formulations; and suggest that Okra powder could be further developed for commercial purposes.

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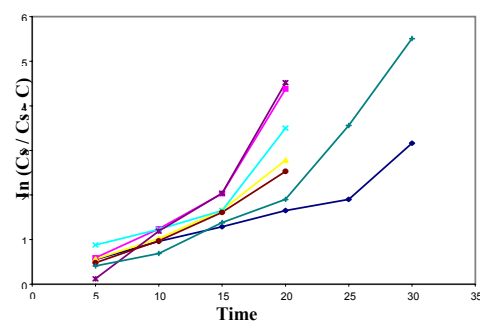


FIG 2. In (Cs/Cs - C) vs time plots for Metronidazole tablets formulated with FOP-OV

◆,0%;■,2.5%;▲,5.0%;×,7.5%;×,10%;●,12.5%;+,15.0%

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