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Okra gum- an economic choice for the amelioration of capping and lamination in tablets

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ABSTRACT

This work was aimed at comparing the mechanical and release properties of paracetamol tablets formulated with okra gum (OKG), povidone (PVP), gelatin (GEL), and hydroxypropylmethyl cellulose (HPMC) as wet binders. Each was separately employed at 1.0 - 5.0%w/w to granulate powder mix of paracetamol (82%), lactose (8%), and corn starch BP (10%). Compacts with and without centre holes were made with 500mg of granules compressed at 7.5 arbitrary units. Relevant quality control tests were performed on the tablets and the results compared. Friedman's test and regression analysis were employed to analyze binder effectiveness and economy on paracetamol tablet formulation. Results showed tablets' tensile strengths to be in the order: HPMC > GEL > OKG > PVP. All the tablets (except those formulated with 1.0%w/w HPMC) passed the friability test. Friedman's test revealed OKG as the most effective binder while regression analysis proved OKG to be the most economical binder with respect to reduction of BFI values ($P < 0.05$) which is directly related to binders' abilities to ameliorate capping and lamination in tablets. The dissolution profiles of tablets formulated with OKG were good at binder concentrations of 1 - 2 %w/w and closely followed those of tablets formulated with PVP. Beyond 2 %w/w binder concentration the profiles declined, in comparison to those of PVP yet better than those of GEL, and HPMC. At 1.0%w/w concentration, OKG reduced the BFI of paracetamol tablets to an acceptable level (0.296), and with a dissolution profile similar to that of PVP formulated tablets, it has proved to be more effective and economical than PVP which imparted a similar BFI values to the tablets at concentration thrice that of OKG. OKG is therefore recommended as an alternative to PVP, an expensive binder.

Keywords: Economical binder, Okra gum, Povidone, Gelatin, HPMC.

INTRODUCTION

Paracetamol tablets are the most consumed analgesic and antipyretic tablets in Nigeria. For this reason, majority of the indigenous pharmaceutical manufacturers produce paracetamol tablets. The ingredients relevant to the production exercise are virtually imported. Although there are many sources of pharmaceutical raw materials in Nigeria, the drawback has always been the

inability of the local industries to generate pharmaceutical grade products due to production costs, and some toxicological studies required by regulatory authorities. However, okra pods which are a potential source of pharmaceutical raw material(s) in Nigeria, whose production cost is low, and which may not require toxicological studies since they are eaten either raw or cooked by Nigerians [1], yield a suitable gum that is useable as safe pharmaceutical raw material; but has been neglected over the years. Okra pods are fruits of the plant *Abelmoschus esculentus* L. moench, family Malvaceae. World production of Okra as fruit vegetable is estimated at 6000000 tons/year. In West Africa, it is estimated at 500000 - 600000 tons/year [2]. In Nigeria okra is grown basically in all states of the federation both as rain fed and irrigated crops. In the peak season, it is produced in large quantities much more than what the local populace can consume, thus leading to heavy wastages [3]. Okra gum, which is a natural polymer, has advantage over synthetic and semi-synthetic polymers, in that it is cheap and easily available, non-irritant, biodegradable, biocompatible, and eco-friendly [4]. Okra gum has been investigated as a binding agent in tablet dosage forms, and has been shown to produce tablets with good hardness, friability and drug release profiles [5]. It has also been utilized as a plasma expander [2]. The indigenous pharmaceutical manufacturers should therefore exploit this economic source of excellent pharmaceutical excipient that has been studied [6, 7, 8].

Paracetamol powder is an elastic material, and therefore needs a good binder for its formulation into tablets in order to forestall the incidence of capping and lamination (the major problems encountered by paracetamol tablet manufacturers). Some manufacturers have employed various binders, for example, povidone (PVP), corn starch, acacia, hydroxypropylmethyl cellulose (HPMC) either alone or in-combination with other binder(s) in the formulation of paracetamol tablets [9].

Measurable mechanical properties of tablets include: tensile strength, packing fraction, friability, disintegration time, bonding index, strain index, etc [10]. In conventional tablets, binders' seemingly excellent ability to hold powder particles together as estimated by the bonding index is not sufficient to guarantee that capping and lamination, very annoying problems in tablet production, will not occur in the formulation. It is this realization that informed the introduction of brittle fracture index (BFI) by Hiestand and his colleagues in 1977 to estimate the ability of materials to ameliorate capping and lamination in tablets [11]. Bond strength and lamination tendencies are two important mechanical properties of tablets that are measurable by tensile strength (TS) and brittle fracture index (BFI) value respectively [12]. All literature search on the binding property of okra gum showed that no researcher has worked on estimating the ability of the gum to forestall the incidence of capping and lamination in tablets. It is based on this and the quest to explore local economic alternatives for excellent binders that this research was designed. In this study therefore, the mechanical and dissolution properties of paracetamol tablets formulated with Okra gum as binder are compared with those of paracetamol tablets formulated with PVP, gelatin, or HPMC as binder.

MATERIALS AND METHODS

Paracetamol powder (Mallirickrodt Inc., USA), corn starch BP (Sigma – Aldrich, USA) – disintegrant, D (+) – lactose monohydrate (Fluka, Netherlands) – filler, okra gum (extracted from okra pods by the method described by Nasipuri, et al [6], PVP K15 (Fluka, USA), gelatin [gel strength (Bloom): 160] (Fluka Germany), HPMC-viscosity: 2600 mPa.s (Sigma, USA), talc (BDH Chem., UK) — lubricant, liquid paraffin (Mopson Pharm., Nigeria), other reagents are of analytical grade.

Preparation of granules

250g batches of a basic formulation of paracetamol powder (82% w/w), lactose (8% w/w) and Corn starch B.P. (10% w/w) were dry – mixed for 10 minutes in a planetary mixer (Model A 120, Hobart Manufacturing CO, UK), moistened with the appropriate amount of binder (okra gum, gelatin, PVP, or HPMC) solution prepared according to the methods reported by previous researchers [13,14], (except that the volume of the solutions was maintained at 30 ml) equivalent to 1.0, 2.0, 3.0, 4.0 and 5.0% w/w in the final granules and granulated by wet massing with mortar and pestle. The homogeneous wet mass was then screened through a 1400 μ m sieve and the wet granules dried in a hot air oven (Unitemp LTE Scientific Ltd Great Britain) at 50⁰C for 18 hours. Thereafter, the dried granules were screened through a 600 μ m sieve in order to generate uniformly sized granules [15] and stored in air tight containers over silica gel before tableting.

Tests conducted on the granules.**Moisture content.**

The moisture contents of the granules were determined according to BP 2009 method [16], and the results ranged from 2.85 % - 3.15 %.

Determination of granule density

Granule density of each formulation was determined using the fluid displacement method [17, 18], and applying the equation [19]:

$$\rho_g = \left[\frac{w}{(a+w)} \right] SG \quad \dots (1)$$

where

ρ_g = granule density in grams per cubic centimeter.

w = granule weight in grams.

SG = liquid paraffin specific gravity = 0.802.

a = pycnometer + liquid paraffin weight in grams.

b = pycnometer + liquid paraffin + granule weight in grams.

Preparation of tablets

Immediately before tableting, each batch of granules was mixed with 0.5% w/w of talc. Tableting was done with a single punch tableting machine (Kilian Frankfurt Germany) which has a flat punch surface of diameter 12.55mm. Tablets were made by weighing accurately 500mg of granules and carefully transferring them into the die, and then compressing manually at a pre-determined pressure of 7.50 arbitrary units, with the pressure held on the granules for 30 seconds before releasing to allow consolidation to occur. The tableting procedure was repeated for tablets with center hole, 1.5mm (made with the upper and lower adapters having a hole and a pin at their centres respectively) [20]. Prelubrication of the die and punches in each stage was done by compressing some powder of pure talc before the granules were compressed [21]. And the tablets were stored in air tight containers over silica gel for 72 hours before the relevant tests were conducted.

Tests conducted on the tablets.**Tablet weight and dimension measurements**

Tablet weights were determined using Electronic balance (Mettler Toledo B154, Switzerland) while the dimensions were measured with Mitutoyo gauge (Model 10C – 1012 EB Japan), to

within $\pm 1\text{mg}$ and $\pm 0.01\text{mm}$ respectively. All the measurements were made in triplicates and the means used in relevant calculations.

Evaluation of tablet relative density.

Tablet relative density was computed using the equation [20]:

$$RD = \frac{4m}{\pi d^2 t \rho_g} \quad \dots (2)$$

where-

m = tablet weight in grams

d = tablet diameter in centimeters

t = tablet thickness in centimeters

ρ_g = density of the granules in gram per cubic centimeter.

RD = tablet relative density

The relative densities of three tablets selected at random were evaluated for each batch and the same tablets were utilized in the determination of each batch's crushing strength.

Tablet crushing strength and friability tests

Crushing strengths of tablets were determined at room temperature by diametral compression using a hardness tester (Kal Kolb, Erweka Germany). Results were taken from tablets that split cleanly into two halves without any sign of lamination. All measurements were made in triplicates and their means used to calculate the tablets tensile strengths. The percentage friabilities of the tablets were determined using Roche Friabilator (Copley/Erweka, Type, TAR 20, GMBH Germany), operated at 25rpm for 4 minutes.

Evaluation of tablet tensile strength and brittle fracture index (BFI).

Tablet tensile strength was evaluated using the modified Fell and Newton equation [22]:

$$T \text{ or } T_0 = \frac{2F}{\pi dt(1 - e)} \quad \dots (3)$$

where –

T = tablet tensile strength (MN/m^2)

F = the load (MN) applied to cause diametral fracture of the tablet

d = tablet diameter in meters

t = tablet thickness in meters.

e = tablet porosity

$1 - e = \text{RD}$.

Tablet BFI is evaluated by comparing the tensile strengths (T_0) of tablets with a hole (1.5mm) at their centers (an in-built stress concentrator defect) with the tensile strengths (T) of tablets without a hole. BFI is computed with the equation [11]:

$$\text{BFI} = 0.5 \left[\frac{T}{T_0} - 1 \right] \quad \dots (4)$$

Tablet disintegration and dissolution tests

The disintegration times of the tablets were determined in distilled water at $37 \pm 0.5^\circ\text{C}$ using the disintegration tester (Manesty, Model: MK 4, UK). Six tablets were selected at random from each batch and the machine operated till all the tablets disintegrated. The results reported are the means \pm standard deviation.

Before the dissolution test, $10\mu\text{g/ml}$ of paracetamol solution in 0.1N HCl was scanned between 200nm and 800nm using UV-Visible spectrophotometer (UV- 160A Shimadzu Corporation Japan). Maximum absorbance (0.791) was shown at a wavelength of 296nm . Tablet dissolution test was then carried out using the USP XXIII basket method (Erweka Germany Type: DT 80) operated at 50rpm for 30 minutes in 900ml of 0.1N HCl maintained at $37 \pm 0.5^\circ\text{C}$. At 5 minutes intervals, 5ml of dissolution fluid was withdrawn and replaced with 5ml of fresh 0.1N HCl . Each withdrawn sample was filtered and the amount of paracetamol released determined using the UV-Visible spectrophotometer, at 296nm with 0.1N HCl as blank.

Statistical analyses**Friedman's test.**

Friedman's test was employed to test the null hypotheses (H_0): there were no significant differences between the BFI values of paracetamol tablets formulated with okra gum, gelatin, PVP, or HPMC at fixed concentrations within the range $1.0\% \text{w/w} - 5.0\% \text{w/w}$.

Alternate hypothesis (H_A): there are considerable differences between the tablets' BFI values.

Level of significance (α): 0.05.

Friedman test is executed with the formula [23]:

$$X_R^2 = \frac{12}{N_{\text{rows}} N_{\text{columns}} (N_{\text{columns}} + 1)} \sum R^2 - 3N_{\text{rows}} (N_{\text{columns}} + 1) \quad \dots \quad (5)$$

where-

N_{rows} = number of rows in table

N_{columns} = number of columns in table

R = sum of ranks in each column

X_R^2 = calculated Friedman's statistic.

Regression analysis

This was carried out using Microsoft excel 2007 regression analysis tool pack.

RESULTS

Table 1: Effect of binder concentration on tensile strength (TS), friability, BFI and disintegration times of tablets.

Binder conc. (% w/w)	TS (MN/m ²)	BFI	Friability (%)	Disintegration time (min)
Okra gum				
1.0	0.90±0.222	0.2960	0.97	0.69±0.054
2.0	1.13±0.131	0.2292	0.84	1.22±0.204
3.0	1.47±0.265	0.2238	0.75	1.49±0.204
4.0	1.55±0.131	0.2015	0.72	2.78±0.320
5.0	1.61±0.137	0.1667	0.67	3.54±0.234
Povidone				
1.0	0.85±0.145	0.4362	0.95	0.51±0.025
2.0	1.05±0.182	0.3614	0.88	0.86±0.067
3.0	1.33±0.159	0.2622	0.78	0.97±0.167
4.0	1.47±0.289	0.2408	0.66	1.61±0.192
5.0	1.65±0.157	0.2057	0.65	3.70±0.200
HPMC				
1.0	1.03±0.110	0.3517	2.05	8.63±0.327
2.0	1.46±0.229	0.3131	0.93	74.61±0.386
3.0	1.56±0.108	0.2857	0.75	155.92±0.952
4.0	1.64±0.202	0.2284	0.70	410.88±2.589
5.0	1.77±0.208	0.2064	0.65	>480.00
Gelatin				
1.0	0.88±0.142	0.3376	0.83	0.51±0.084
2.0	1.24±0.198	0.3198	0.75	1.24±0.051
3.0	1.41±0.314	0.2383	0.75	5.00±0.667
4.0	1.58±0.307	0.2147	0.70	6.61±0.264
5.0	1.83±0.356	0.2081	0.64	11.28±0.752

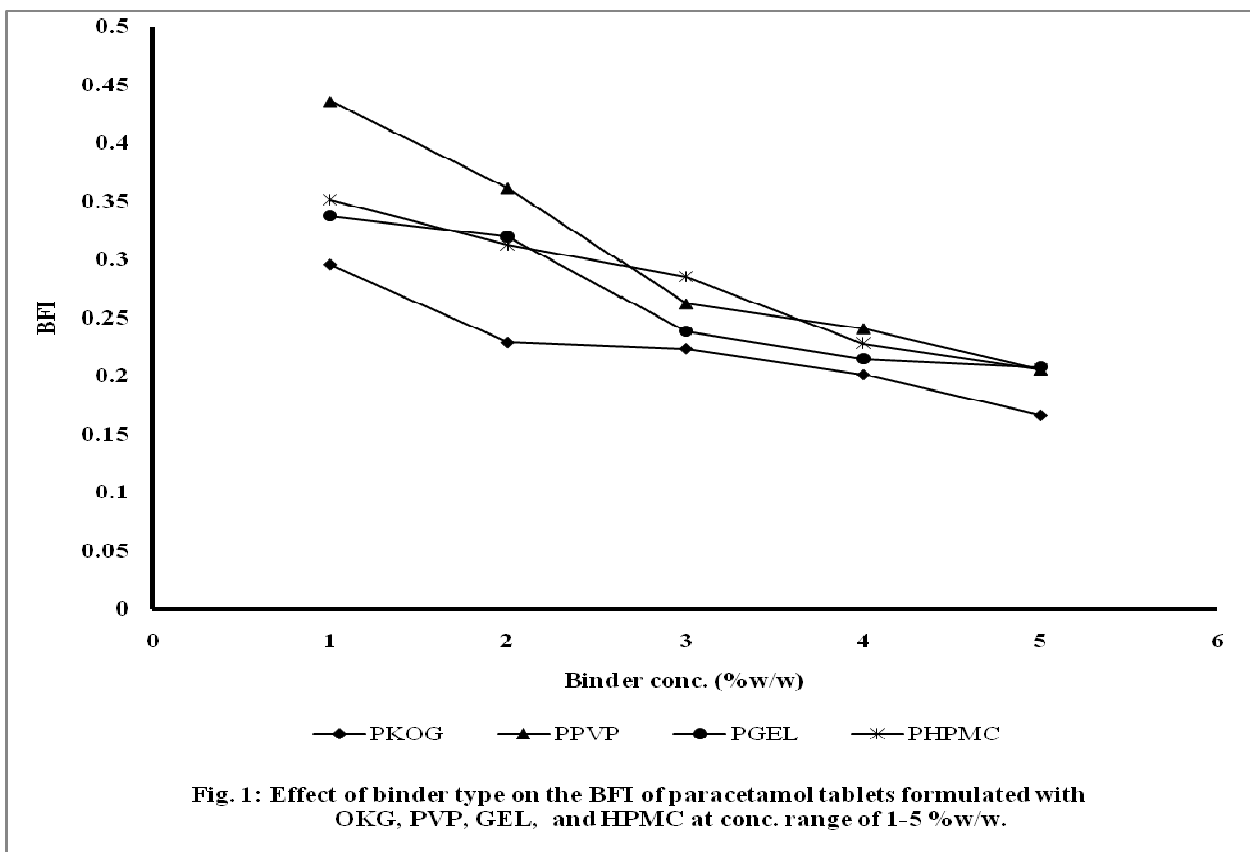


Fig. 1: Effect of binder type on the BFI of paracetamol tablets formulated with OKG, PVP, GEL, and HPMC at conc. range of 1-5 %w/w.

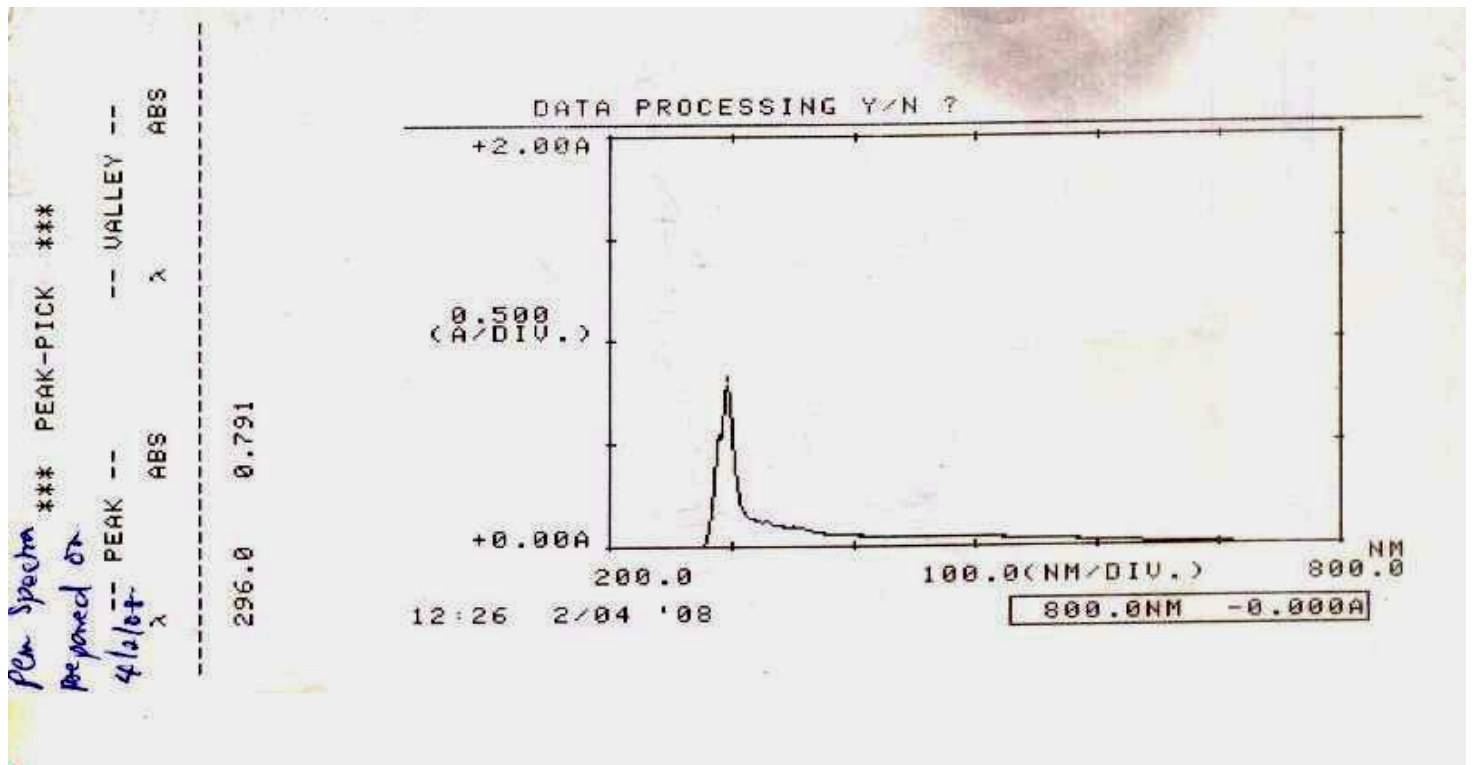


Fig. 2: Paracetamol spectrum in 0.1 N HCl.

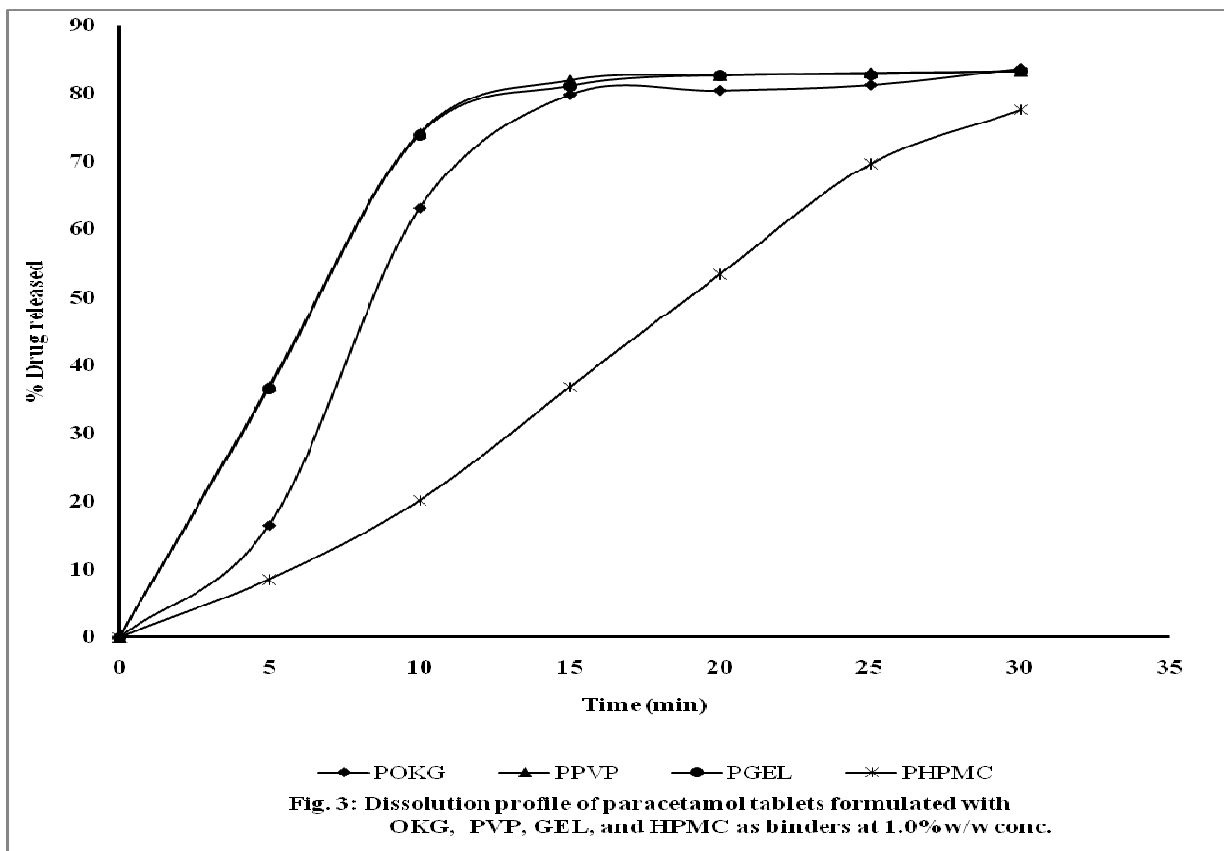
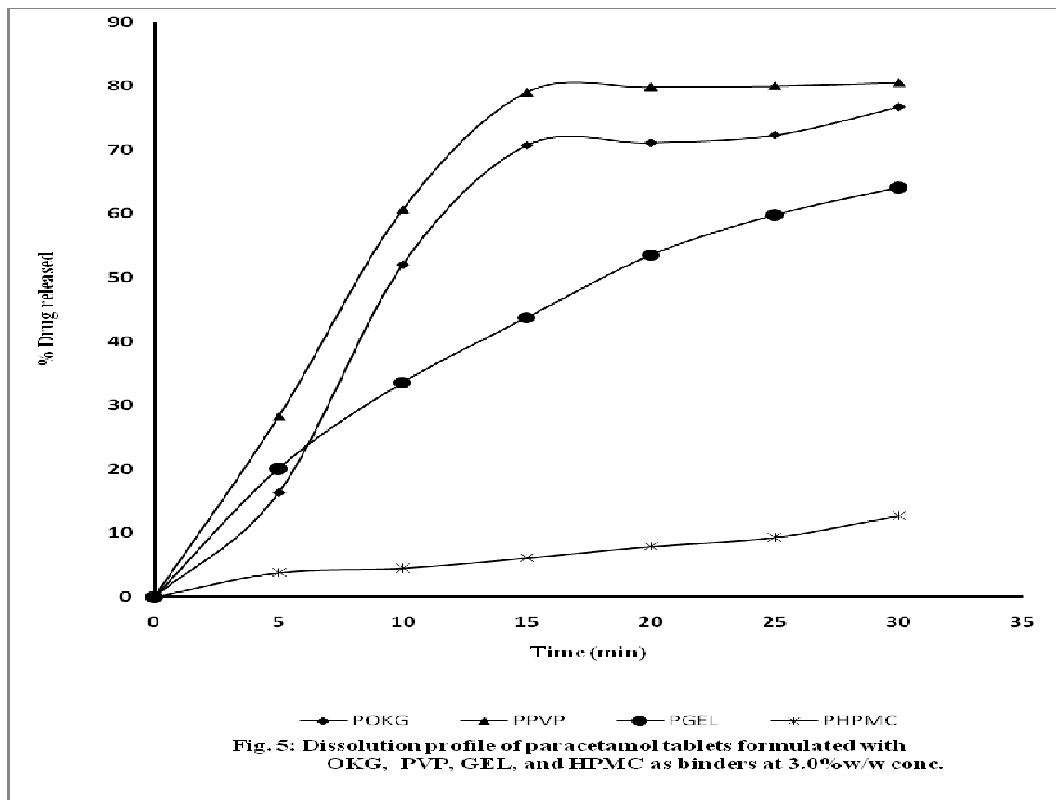
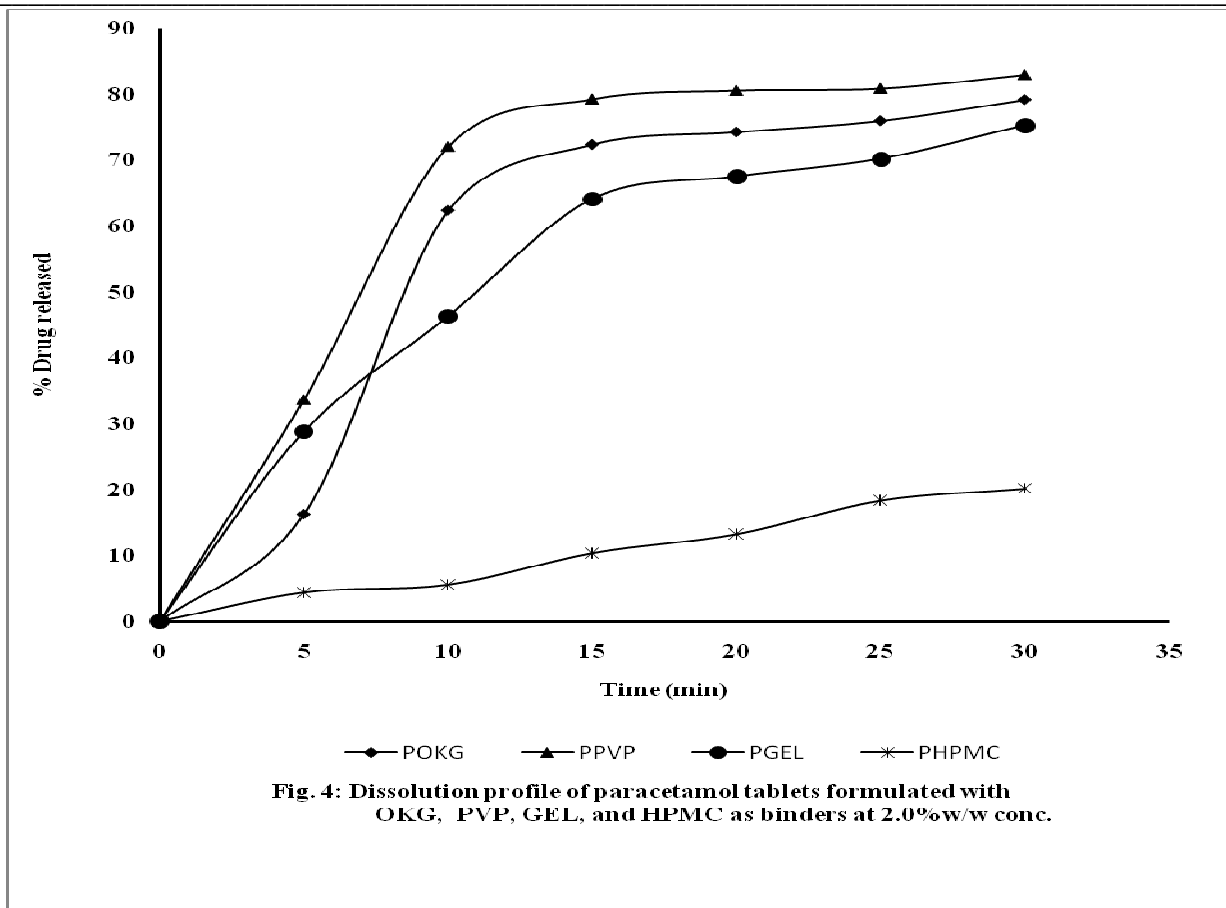


Fig. 3: Dissolution profile of paracetamol tablets formulated with OKG, PVP, GEL, and HPMC as binders at 1.0%w/w conc.



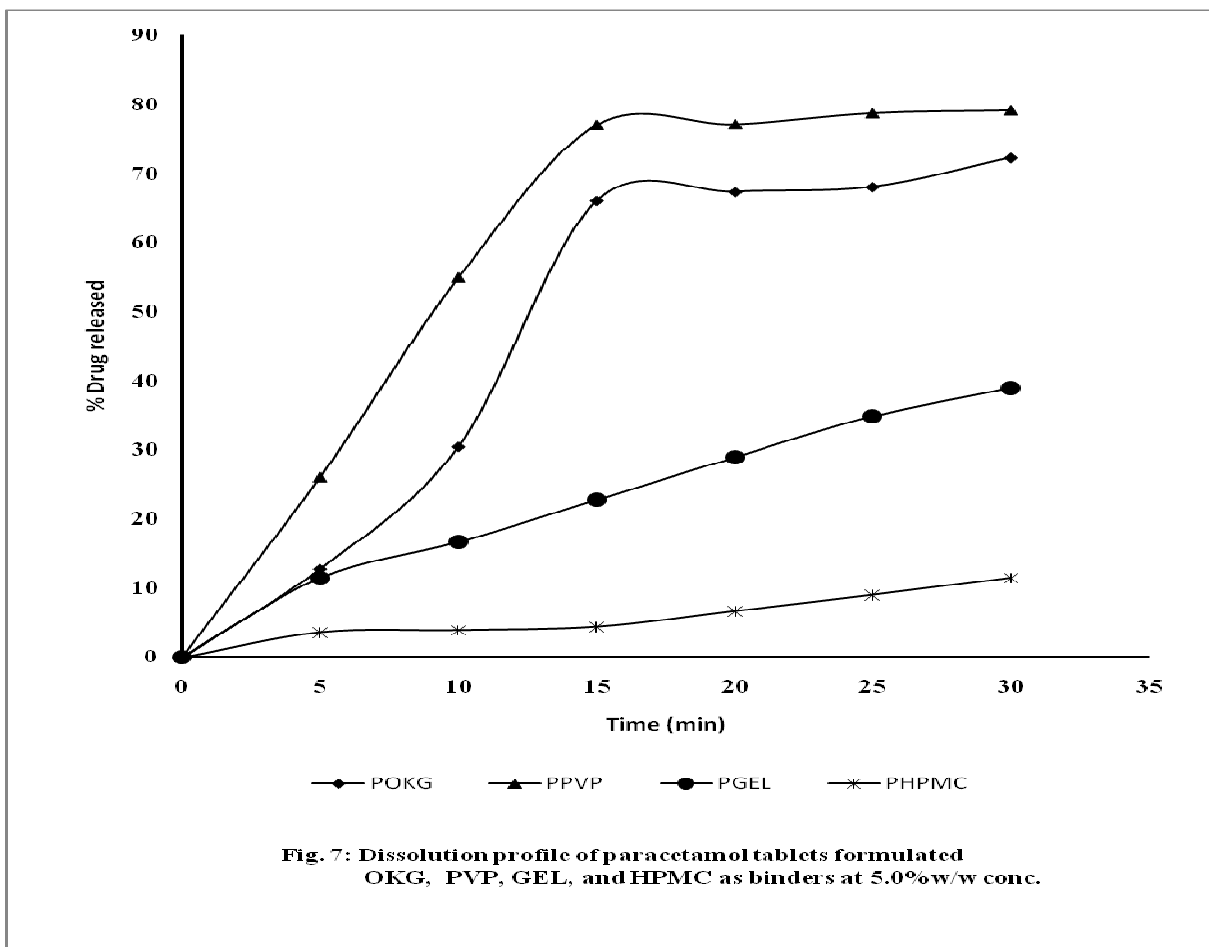
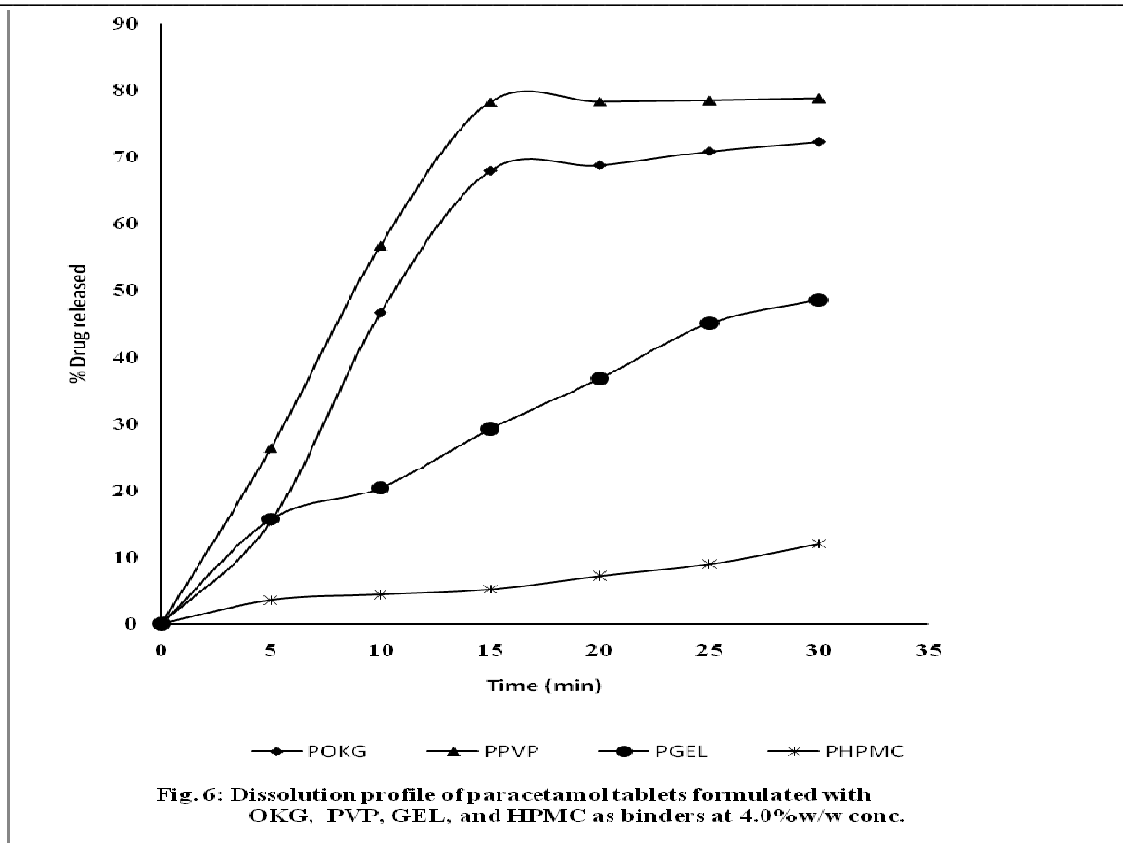


Table 2: Summary of regression analyses of BFI on binder concentration for paracetamol tablets.

Tablet Type	R	R ²	Slope
POKG	0.9544	0.9108	-0.0286
PPVP	0.9675	0.9360	-0.0582
PHPMC	0.9921	0.9843	-0.0376
PGEL	0.9482	0.8990	-0.0364

POKG- Okra gum as binder; PPVP- Povidone as binder; PHPMC- Hydroxypropylmethyl cellulose as binder. PGEL – Gelatin as binder

DISCUSSION

Table 1 shows the effect of binder concentration on tablet tensile strength, brittle fracture index, friability, and disintegration time. It is evident that tablet tensile strength increased with increase in binder concentration. Tablet tensile strength is a function of the strength of the bonds between the powder particles that form the tablet lattice structure. Generally, the higher the bond strength, the higher the tensile strength of the compact [11]. Tablets tensile strengths followed the order- HPMC > GEL > OKG > PVP > ACG. This order however does not imply directly that the ability to withstand post compaction stress or handling by the respective batches follows as well. Tensile strength has been reported to be a direct indication of bond strength within the tablet [11, 12]. A tablet's tensile strength may directly influence its disintegration time depending among other factors on the type of disintegrant used in its formulation. This assertion is also evident in Table 1 where tablets disintegration times are in the order of their tensile strengths. Disintegration times of tablets are affected by the viscosity and solubility of their binding agents. This therefore explains the long disintegration times of tablets containing HPMC as binder. Although gelatin's viscosity is lower than that of okra gum [24, 25, 26], it is less soluble at 37⁰ C than okra gum, and this explains the higher disintegration times of tablets formulated with it as binder. Table 1 also shows that all the formulations' friability values are less than 1%, which is the official requirement [27], except for tablets formulated with 1%w/w HPMC. The reason(s) for this failure is not yet apparent. It may therefore be stated that high tensile strength does not necessarily translate to low friability in tablets.

Tablets brittle fracture indices displayed inverse relationship to binder concentration. BFI is a measure of the ability of the material under test to relieve stress (associated with capping and lamination) by plastic deformation. A low BFI value (close to zero) indicates the ability of the material to relieve localized stress, whereas a value tending to 1 implies a high tendency for capping and lamination to occur. Since BFI is an inverse measure of localized stress relief, it implies that the ability of the binders to reduce the tendency of paracetamol tablets to cap or laminate increased as binder concentration in granules increased. This they achieved by imparting plasticity on otherwise elastic natured paracetamol powder. It therefore follows that the lower the BFI value imparted by the binder, the higher is the binder's ability to prevent capping and lamination in tablets. Among the four binders utilized in this study, okra gum imparted the lowest BFI values on paracetamol tablets, and this indicates that it relieved localized stress in tablets better than gelatin, PVP, or HPMC. Furthermore, a plot of BFI as a function of binder concentration (Fig.1), and the summary of the regression analysis of BFI on binder concentration (Table 2) reveal more on the comparative effectiveness and economy of the different binders on the formulation of paracetamol tablets. There was a sharp reduction in BFI as the concentration of povidone was increased from 1.0 – 5.0%w/w. Reduction in BFI with increase in HPMC or gelatin concentration was not as sharp as that of povidone, while that for okra gum was very minimal from 2.0 – 4.0%w/w. This implies that for okra gum there is no need for increase in its concentration beyond 2.0%w/w in order to formulate tablets with

excellent mechanical and release properties, while the use of povidone alone may require up to 5.0%w/w to attain the same level of BFI reduction. This claim is further emphasized by the regression analyses result (Table 2) which reveals that for every increase in binder concentration, okra gum reduces BFI by the least value when compared to the other binders as shown by the values of their slopes. The use of okra gum as a binder beyond 1 %w/w concentration in the formulation of conventional tablets may therefore be described as an unpardonable wastage since it does not have any positive impact on the quality of such tablets. Increase in the concentration of HPMC or gelatin to achieve good BFI is desirable but that may negatively affect the release profile for conventional tablets [28]. The application of Friedman's test reveal that there were statistically significant differences between the BFI values of paracetamol tablets formulated with the different binders employed in the study at 0.05 level of significance. The difference was caused by okra gum which consistently imparted the lowest BFI values to paracetamol tablets at every concentration. This therefore further emphasizes the superiority of okra gum to PVP, gelatin and HPMC in its ability to ameliorate capping and lamination in paracetamol tablets.

The in-vitro drug release profiles of the tablets are depicted in Fig. 3 – 7. Tablets formulated with povidone generally released the highest amount of drug from 5 minutes to 30 minutes interval. However, the amount of drug released by tablets formulated with okra gum closely followed those of povidone each time at binder concentrations of 1 – 2 %w/w. This is consistent with the report of previous researchers [29, 30]. Fast disintegration is highly desirable for conventional tablets. Disintegration of tablets has been reported to influence the dissolution process, since it assists in increasing the area of contact between the solid and liquid [31]. And as shown in Table 1, tablets formulated with povidone disintegrated faster than those formulated with Okra gum, gelatin, or HPMC. This and the high solubility of povidone in water even at room temperature explain the higher dissolution profile of tablets formulated with it. Okra gum which is also water soluble at room temperature also did not negatively affect the release profiles of tablets formulated with it at low binder concentrations (1 – 2 %w/w). This quality plus its ability to reduce BFI to an acceptable level at 1%w/w concentration, coupled with its consistent availability and inexpensiveness depict it as a better and more economical binder for paracetamol tablets. The patterns of dissolution profiles of tablets formulated with gelatin are not better than those of okra gum. This is consistent with the disintegration times of the tablets. Tablets formulated with HPMC generally displayed slow release beyond 1 %w/w concentration, and this is not surprising bearing in mind the viscosity of HPMC, coupled with the report that the use of water alone as granulating liquid has a tendency to decrease the amount of paracetamol released from tablets formulated with HPMC [32]. But, unlike okra gum, at this low concentration, the BFI and friability of the tablets were not acceptable. At 1.0%w/w binder concentration both povidone and okra gum formulated tablets released 80% of their drug content (t_{80}) in 15 minutes. Thus as okra gum imparted lower BFI (0.2960) than povidone (0.4362) and had similar t_{80} at this binder concentration, it can successfully be used in place of povidone in conventional tablet formulations at 1.0%w/w concentration to produce tablets with acceptable mechanical and drug release profiles. Thus it is recommended that okra gum be employed in the formulation of conventional tablets at concentration range of 1.0 – 2.0%w/w since beyond this range, reduction in BFI is not appreciable, and drug release may not compare favorably with povidone. Furthermore, as okra gum is cheaper and easier to source, and a much smaller amount is necessary in conventional tablet formulation, it is strongly recommended also that our indigenous manufacturers should invest in its exploration and exploitation.

CONCLUSION

The mechanical properties of paracetamol tablets formulated with okra gum as binder at the concentrations used are similar to those of povidone, gelatin, and HPMC. Okra gum is superior to the three binders in its ability to reduce brittle fracture tendency in paracetamol tablets. And because it can achieve very good drug release profile and mechanical properties at low binder concentration range (1.0%w/w – 2.0%w/w) it should be better explored and exploited as an alternative to povidone in tablet formulation since its production would generally be cheaper; thus invariably leading to lower cost of tablet production.

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