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Full Length Research Paper

Physicochemical characterisation of *Irvingia wombolu* gum in tramadol encapsulated granules

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The objectives of the work were to evaluate the binder properties of gum from *Irvingia wombolu* seed cotyledons and to compare with sodium carboxymethylcellulose (SCMC) in tramadol encapsulated granules. Tramadol granules was formulated by wet granulation using gum derived from the seed cotyledons of *I. wombolu* as binder at concentrations of 2.5, 5.0, 7.5, 10.0 and 15.0% w/w. The binder properties of the gum were compared with that of SCMC. The flow properties of the granules were studied by direct and indirect methods. The tramadol capsules were evaluated using necessary official tests. The phytochemical and physicochemical properties of the gum were also studied. The results showed that tramadol granules exhibited good flow for the production of quality capsules. Tramadol capsules formulated with *Irvingia wombolu* gum and SCMC, respectively complied with BP specification for capsules weight uniformity with percentage deviations below 10%. Capsule disintegration time ranged from 4.80 ± 0.43 min to 5.90 ± 0.45 min for tramadol capsules formulated with *I. wombolu* gum and were not significantly affected by concentration of gum in the formulation ($p < 0.05$). However, tramadol capsules formulated with *I. wombolu* gum exhibited faster disintegration time than SCMC ($p < 0.05$) whose disintegration time occurred at 14.20 ± 0.87 min. The results of phytochemical analysis of *I. wombolu gum* showed that the gum contains alkaloids, flavonoids, saponin, tannins and glycosides. Therefore, natural gum from *I. wombolu* has good potential to be used in formulating normal release tramadol capsules.

Key words: *Irvingia wombolu* gum, physicochemical characterization, micromeritic studies, capsule production.

INTRODUCTION

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine that is a weak μ-opioid receptor agonist (Howard and Huda). It is indicated for the management of moderate to moderately severe pain including chronic pain and pain associated with molar extraction in adults (Wantana et al., 2011). Tramadol is an effective and well-tolerated agent to reduce pain resulting from trauma, renal or biliary colic and labour, and for the management of chronic pain of malignant or nonmalignant origin, particularly neuropathic pain (Wantana et al., 2011).

Irvingia wombolu commonly called bush/wild mango, or dika nut, is an edible Africa indigenous fruit tree that produces edible fruits and seeds (Atangana et al., 2002; Harris, 1996). *Irvingia* belongs to the family Irvingiaceae; the fruit of *I. wombolu* is sour and is consumed locally and the edible kernels are used for culinary purposes (Fajimi et al., 2007). In Nigeria, the kernels are used as a condiment and are highly valued for their food thickening properties (Ndjouenekeu et al., 1996; Fajimi et al., 2007) in preparing “ogbono” or draw soup. Gums from plants are mainly long chain, straight or branched chain polysaccharides that contain hydroxyl groups which bond to water molecules (Emeje et al., 2008). These gums are generally non-toxic and widely available, hence the continued interest (Emeje et al., 2008). A number of plant gums have been investigated as binding, suspending or

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emulsifying agents in both solid and liquid dosage formulations (Chukwu et al., 1994; Nasipuri et al., 1999; Odeku and Itiola, 1998; Emeje et al., 2008). Binders confer structural strength required by granules during processing, handling, packaging and transportation. The widening availability of natural gums with specific characteristics offers flexibility of application with respect to improving the bioavailability of drugs and manipulating their release profile (Momoh et al., 2011). Also, the use of synthetic polymer matrix materials often goes along with detrimental effects on incorporated drug during manufacturing of formulations or during the erosion of the polymers after application (Reithmeir et al., 2001). The aim of the work is to formulate tramadol encapsulated granules using a natural gum from the seed cotyledons of *I. wombolu* and to evaluate the *in vitro* properties of the capsules.

MATERIALS AND METHODS

Chemicals and reagents

Lactose (Merck, Germany), sodium carboxymethylcellulose, acetone (BDH, England), magnesium stearate, tramadol (May and Baker, England), distilled water (Lion water, Nsukka, Nigeria) were used for this study. *I. wombolu* seed gum was obtained from a batch processed in our laboratory. All other reagents and solvents were of analytical grade and were used as supplied.

Extraction of *I. wombolu* gum

I. wombolu seed were purchased from the market of Nsukka, Enugu State, Nigeria in the month of June, 2010. The plant material was authenticated by Mr. A.O. Ozioko, a consultant taxonomist with the International Center for Ethnomedicine and Drug Development (InterCEDD) Nsukka. The voucher specimen of the plant studied was kept in the herbarium of the Department of Pharmacognosy and Environmental Medicines, University of Nigeria, Nsukka. *I. wombolu* seeds were milled using an equipment of hammer mill type (500# grinder/Fuyu Metal, Linyi Fuyu Metal Products Co., Ltd, China) and soaked in water containing 1% sodium metabisulphite for about 12 h, it was filtered and the gum was precipitated using acetone. The precipitated gum was dried for 2 h in a tray dryer (Manesty Ltd, Liverpool, England) at 40°C. The dried gum was milled in an end runner mill (Pascal Engineering Co Ltd, England) and finally passed through 55 mm sieve (Turgens & Co., Germany).

Phytochemical screening

Phytochemical tests were carried out on the powdered gum for the presence of alkaloids, tannins, saponins, flavonoids, resins, oils, steroids, glycosides, terpenoids, acid compounds, carbohydrates, reducing sugars and proteins. The tests were carried out using standard procedures of analysis (Harborne, 1993; Sofowora, 1993; Trease and Evans, 2002).

Rheological properties of *I. wombolu* gum

A 3 %w/v of *I. wombolu* gum was prepared and the viscosities were determined at temperatures of 25, 40, 80, 60 and 100°C, respectively (Onyechi, 2008).

Solubility

The solubility of the *I. wombolu* gum was tested in water (cold and hot), n-hexane, petroleum ether, chloroform ethyl ether, acetone, ethanol and methanol.

Preparation of granules

Granules were prepared by wet granulation method using *I. wombolu* gum as binders at concentrations 2.5, 5.0, 7.5, 10.0 and 15% w/w. Details of granulation are given in Table 1. Lactose used as filler and tramadol were mixed for 10 min in a tumbler mixer. The powder mixtures were moistened with the appropriate amount of binder solution. The homogeneous wet mass was then screened through a 1.7 mm sieve and the wet granules dried in a hot air oven at 55°C for 1 h. Thereafter, the dried granules were screened through a 1.0 mm sieve (Lachman et al., 1990; Shendge et al., 2010).

Characterisation of granules

Bulk and tapped densities

A 25 g quantity of each batch of tramadol granules was placed in a 100 ml measuring cylinder. The volume occupied by the sample was noted as the bulk volume. The bulk density was calculated as shown in Equation 1:

$$\text{Bulk density } (\ell_B) = \frac{\text{Mass of powder (M)}}{\text{Bulk volume of powder } (V_B)} \quad (1)$$

The cylinder was tapped on a wooden platform by dropping the cylinder from a height of one inch at 2 s interval until there was no change in volume reduction. The volume occupied by the sample was then recorded as the tapped volume. The tapped density was calculated using the formula:

$$\text{Tapped density } (\ell_T) = \frac{\text{Mass of powder (M)}}{\text{Tapped volume of powder } (V_T)} \quad (2)$$

Flow rate and angle of repose

A funnel was properly clamped on to a retort stand. The funnel orifice diameter, base diameter and efflux tube length were appropriately measured. A 25 g quantity of the granule was placed into the funnel with the funnel orifice closed with a shutter. The time taken for the entire sample in the funnel to flow through the orifice was noted. The flow rate was gotten by dividing the mass of the sample by the time of flow in seconds. The dynamic angle of repose was determined by measuring the height of heap of powder formed using a cathetometer; the radius was obtained by dividing the diameter by two. Angle of repose (ɵ) for each granule sample was calculated using Equation 3 (Aulton, 2007; Ngwuluka et al., 2010):

$$\Theta = \tan^{-1} \frac{\text{height of powder heap}}{\text{radius of powder}} \quad (3)$$

Table 1. Composition of tramadol capsules.

Ingredient	Quantity/capsule (mg)				
	F1	F2	F3	F4	F5/G
	2.5% binder	5.0% binder	7.5% binder	10.0% binder	15.0% binder
Tramadol	50.0	50.0	50.0	50.0	50.0
Binder*	2.5	5.0	7.5	10.0	15.0
Magnesium stearate	1.0	1.0	1.0	1.0	1.0
Lactose qs	100.0	100.0	100.0	100.0	100.0

**Irvingia wombolu* gum, sodium carboxymethylcellulose (SCMC).

Table 2. Results of phytochemical constituents of *I. wombolu* seed gum.

Phytochemical constituent	Remark†
Alkaloids	+
Saponins	+
Reducing sugars	-
Tannins	+
Glycosides	+
Flavonoids	+

†- Absent, + present.

Compressibility index and Hausner's quotient

Carr's compressibility indices (%) of the granules were obtained using the formula (Aulton, 2007; Ngwuluka et al., 2010).

$$\text{Carr's index}\ (\%) = \frac{\ell_T - \ell_B}{\ell_T} \times 100 \quad (4)$$

While Hausner's ratio was obtained using the formula:

$$\text{Hausner's ratio} = \frac{\ell_T}{\ell_B} \quad (5)$$

Where ℓ_T and ℓ_B are tapped and bulk density, respectively.

Preparation of capsules

Initially, granules were treated with magnesium stearate (lubricant) and the capsules were filled manually using 100 mg of tramadol granules per capsule (Ofoefule, 2002).

Evaluation of capsules

Disintegration time test

Disintegration time test was conducted using an Erweka ZT 120 basket and rack assembly and 0.1 N HCl maintained at 37.0 ± 1.0°C as the disintegration medium. Ten capsules from each batch were used for the test and the procedure being as stipulated in the British Pharmacopoeia (BP) (2009).

Uniformity of mass

Twenty capsules were randomly selected from each batch. The content of each capsules were weighed individually using an electronic balance (Ohaus Adventurer, China) and the individual weights recorded. The mean weight, standard deviation and percentage deviation were calculated (BP, 2009).

Statistical analysis

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) version 14.0 (SPSS Inc. Chicago, IL.USA). All values are expressed as mean ± standard deviation (SD). Data were analysed by one-way Analysis of Variance (ANOVA). Differences between means were assessed by a two-tailed student's T-test. $P < 0.05$ was considered statistically significant.

RESULTS

Phytochemical constituents of *I. wombolu* gum

The results of the phytochemical analysis of the gum are shown in Table 2. The results revealed that the gum contains alkaloids, saponins, tannins, flavonoids and glycosides in substantial quantities. Reducing sugars was however not found in the gum.

Solubility

I. wombolu gum was soluble in hot and cold water (0.1% w/v). However, the gum was insoluble in n-hexane, petroleum ether, chloroform ethyl ether, acetone, ethanol and methanol.

Rheological properties of gum

The effect of temperature on the viscosity of *I. wombolu* gum is shown in Figure 1. From the results, increase in temperature increased the viscosity of the gum. Therefore, this gum could be used as binders in wet granulation without affecting the properties of the gum.

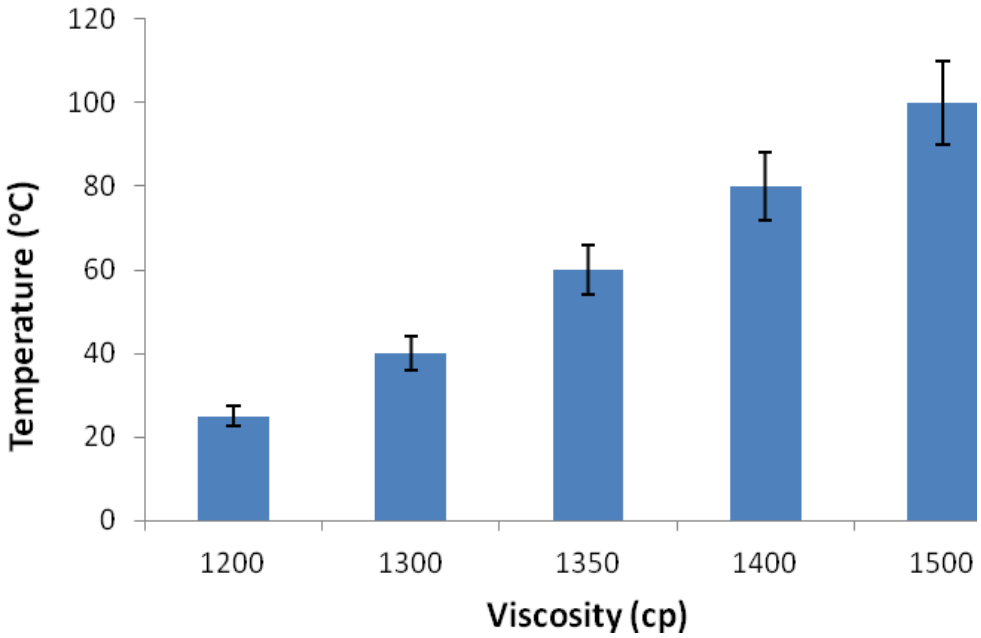

Figure 1. Effect of Temperature on 3% dispersion of the gum.

Table 3. Micromeritic properties of tramadol granules formulated with *I. wombulu* gum.

Batch (%)	ℓ_B (g/ml)*	ℓ_T (g/ml)*	A.R (°)*	H.R	C.I (%)	Flow rate (g/s)
F1 (2.5)	0.43±0.05	0.81±0.09	13.10±0.05	1.88	46.90	0.10
F2 (5)	0. 42±0.03	0.80±0.07	14.00±0.03	1.90	47.50	0.10
F3 (7.5)	0.42±0.11	0.67±0.05	20.10±0.03	1.60	36.30	0.10
F4 (10)	0.39±0.05	0.50±0.07	22.50±0.09	1.25	22.00	0.09
F5 (15)	0.49±0.11	0.78±0.03	19.02±0.17	1.60	37.20	0.09
G (15 SCMC)	0.42±0.17	0.81±0.12	19.65±0.01	1.90	48.10	0.08

Values shown are mean ± SD (*n = 3); F1 to F5: tramadol granules prepared with different concentrations of *I. wombolu* gum, G: tramadol granules prepared with 15% SCMC; ℓ_B and ℓ_T = bulk and tapped densities, AR = angle of repose, HR = Hausner's ratio, CI = Carr's compressibility index, SCMC: sodium carboxymethylcellulose.

Table 4. Weight uniformity of tramadol capsules.

Batch/tablet code (%)	Weight (mg ± CV)*
F1 (2.5)	102.00±1.09
F2 (5)	100.00±0.50
F3 (7.5)	102.00±2.53
F4 (10)	102.00±3.70
F5 (15)	100.00±2.04
G (15 SCMC)	100.00±1.73

*Mean for 20 capsules, F1 to F5: tramadol granules prepared with different concentrations of *I. wombolu* gum, G: tramadol granules prepared with 15% SCMC, $p < 0.05$ was considered significant.

Flow properties of tramadol granules

The results obtained from micromeritic studies presented in Table 3 showed that *I. wombolu* granules exhibited good flowability.

Properties of capsules

Capsule weight uniformity

The results of capsule weight uniformity presented in Table 4 showed that capsule weight ranged from 100.00 ± 0.50 to 102.00 ± 1.09 mg. The results indicate that

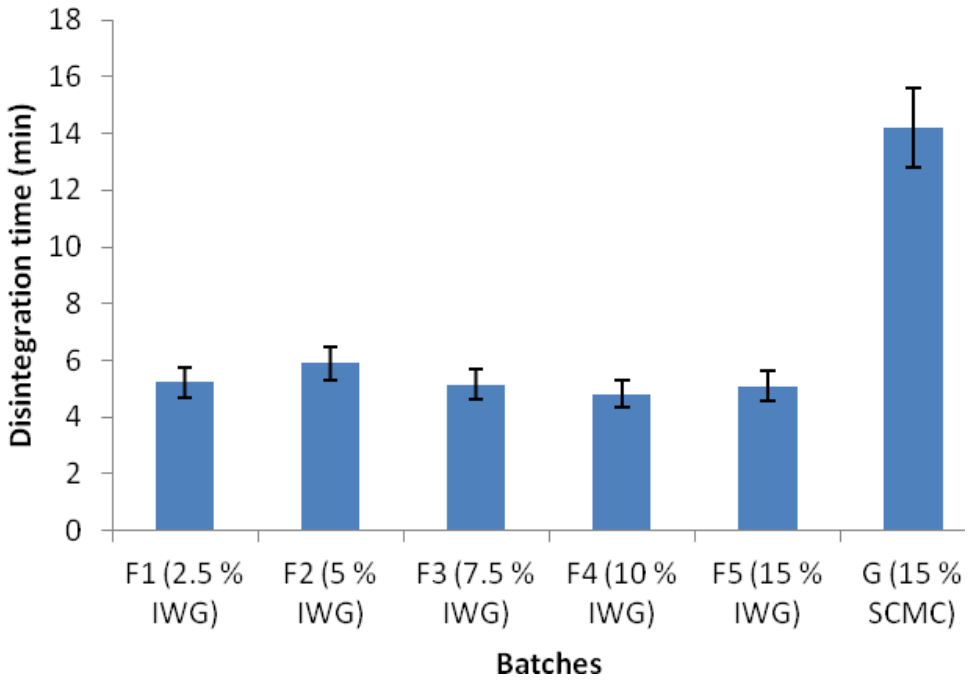

Figure 2. Disintegration time of tramadol capsules; batches F1 to F5: tramadol granules prepared with different concentrations of *I. wombolu* gum, G: tramadol granules prepared with 15% SCMC, $p < 0.05$ was considered significant.

tramadol capsules formulated with *I. wombolu* gum and SCMC, respectively complied with BP specification for capsules weight uniformity.

Disintegration time

The results of capsule disintegration time also presented in Figure 2 showed that tramadol capsules exhibited good disintegration time and complied with BP specifications.

DISCUSSIONS

Phytochemical constituents of *I. wombolu* gum

Phytochemicals are non-nutritive plant chemicals that have protective or disease preventive properties. Plants produce these chemicals substances to protect themselves and they are also believed to protect humans against certain diseases (Edeoga et al., 2005). The medicinal plants that are moderately rich in alkaloids and tannins have potential health promoting effects (Olajide et al., 2000; Jigam et al., 2010). The results revealed that the gum contains important phytochemicals as shown in Table 2.

Flow properties of tramadol granules

The granules from various batches exhibited good micromeritic properties. Angle of repose and flow rate were within the standard acceptable values required for formulation of quality capsules. Values for angles of repose ≤ 30° generally indicate a free flowing material and angles ≥ 40° suggest a poorly flowing material (Yüksel et al., 2007; Momoh et al., 2012). Carr's index (CI) indicates the flowability and consolidation properties of the powder mixtures. When the CI and Hausner's ratio are adequate, the powder flows at minimum bulk density (Yüksel et al., 2007; Momoh et al., 2012). The results of Carr's compressibility index and Hausner's ratio indicated values that were above the limits for good powder fluidity. This may be due to such factor as the nature of granulation and other factors that could lead to false negative results. The flow of powder during manufacturing dictates the quality of the product in terms of weight and content uniformity of the capsules (Yüksel et al., 2007). The measurement of the flow properties of granules is essential in capsule production because variation in particle flow will automatically cause variation in capsule filled weight and active ingredient variation. The flow property of bulk material results from the cohesive forces acting on individual particles such as van der Waals, electrostatic, surface tension, interlocking and friction (Yuksel et al., 2007).

friction (Yüksel et al., 2007).

Properties of capsules

Capsule weight uniformity

Tramadol capsules formulated with *I. wombolu* gum in functionality as a capsule excipient compared favourably with SCMC and complied with BP specification for capsules weight uniformity as their percentage deviations were significantly below 10% (BP, 2009).

Disintegration time

Encapsulated tramadol granules had disintegration time range from 4.80 ± 0.43 min to 5.90 ± 0.45 min for capsules formulated with *I. wombolu* gum and were not significantly affected by concentration of gum in the formulation. However, the disintegration time of tramadol capsules formulated with *I. wombolu* gum were significantly lower than that of SCMC ($p < 0.05$) whose disintegration time occurred at 14.20 ± 0.87 min.

Conclusion

Tramadol capsules were successfully formulated using different concentrations of *I. wombolu* seed gum. The granules exhibited good flow properties that were within limits for good granule flow and hence, for quality capsule production. The weight uniformity and disintegration time of tramadol capsules formulated with *I. wombolu* gum complied with BP specifications as did those of tramadol capsules formulated with SCMC. Therefore, natural gum from *I. wombolu* could be used in formulating normal release tramadol capsules.

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