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Preparation and Evaluation of Matrix Tablet of Metronidazole Using Carnauba Wax

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Authors' contributions

This work was carried out in collaboration between all authors. Author MIA conceived and designed the study and review of manuscript. Author SOE analysis of data and manuscript write-up, author JAA supervision of laboratory works, author QF carried out the laboratory work and author PO co-supervision of laboratory works. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To formulate a sustained release tablet dosage form of metronidazole using carnauba wax as matrix former and binder.
Methods: Batches of metronidazole tablets were formulated by using a combination of melt and wet granulation techniques. The formulated granules were evaluated for their flow properties, while the tablets for their friability, hardness, disintegration time and metronidazole release rate. The effect of varying concentrations of carnauba wax on the formulation was ascertained and compared with a conventional commercial product.
Results: The tablets had friability and hardness values ranging from 0.87-2.98% and 6.66 to 8.08 kp, respectively. Tablet weights did not vary significantly but the disintegration time varied from 2.61 to 4.86 min and the optimal batch of tablets released about 60% of its drug within 2 h as against that of the conventional tablet with a 100% release.

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Conclusion: Carnauba wax can serve as a suitable binder to formulate a sustained release metronidazole tablets to achieve a reduction in the frequency of administration and consequently enhance compliance.

Keywords: Carnauba wax; metronidazole; sustained released; melt granulation.

1. INTRODUCTION

Carnauba wax is a natural wax obtained from the leaves of the palm *Copernicia prunifera.* Its hypoallergenic and emollient properties make it the ingredient of choice in many pharmaceutical and cosmetic formulations where it is used as a thickener. Carnauba wax-based lipophilic matrix tablet has been designed recently to protect drugs such as acetyl salicylic acid from hydrolytic degradation during production [1]. Other goals of preparation include, improved/controlled drug release, reduction of ortho oxidation and possible reduction in the cost of production [2,3].

Method of drug production has also been reported to influence drug performance. Cao et al. [4] compared spray-dried granules (SDT) and directly compressible powdered mixtures (DCT) for sustained release containing highly water-soluble drug potassium citrate both prepared using canauba wax. While the DCT was more efficient for sustained release, the release profile was dependent on the formulation composition and preparation method of the matrix tablet.

Controlled release products are designed to maintain constant therapeutic plasma concentration of the drug within the therapeutic range of the drug over prolonged period [5]. It also enables prolonged and continuous deposition of the drug in the gastrointestinal tract and improves the bioavailability of medications characterized by a narrow absorption window. Various terms has been used to describe these formulations such as prolonged-action, repeat action, sustained release, extended release and delayed release [6]. Even though their differences are not much, they all contribute to the advantages of a reduced frequency of drug administrations, optimal use of drug and increased patient compliance [7-10].

Metronidazole (2-methyl-5-nitroimidazole-1-ethanol) is an oral synthetic nitroimidazole antibiotic medication used for the treatment of infections caused by anaerobic bacteria and protozoa [11]. The high frequency of administration of metronidazole in conventional dosage forms reduce patient compliance and also lead to increased incidence of side effect to the drug. This work is aimed at formulating sustained release tablet of metronidazole using carnauba wax as a binder/matrix former.

2. MATERIALS AND METHODS

2.1 Materials

Metronidazole was purchased from Service Pharmaceutical Co. Ltd, Benin City, Nigeria; magnesium stearate, talc were products from BDH Chemicals, UK, lactose was a gift from DFE Pharma, hydrochloric acid from Sigma, Aldrich, Germany. Carnauba wax was obtained from the laboratory stock in the Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Delta State University, Abraka, Delta State, Nigeria. A commercial brand of metronidazole used as control was purchased from a local pharmacy outlet in Delta State. All other chemicals used were of reagent grade and were used without any further purification.

2.2 Methods

2.2.1 Granulation

The melt granulation method was used in preparing all the batches of metronidazole granules using the calculations shown in Table 1. The required quantities of metronidazole and lactose for each batch were weighed into a mixer and dry mixed for 5 min. The quantity of carnauba wax for each batch was also weighed into a beaker and melted over a hot water bath. Metronidazole-lactose mixture was triturated with the hot melted wax until the oil was uniformly distributed in the mixture. The mixture was allowed to cool and passed through 710 µm mesh sieve to obtain the granules.

All the batches of granules were prepared using this procedure except batches F7-F9 where sufficient quantities of 15% w/v maize starch mucilage and half of the required quantities of maize starch powder as internal disintegrant were mixed with the drug-lactose mixture after trituration with the melted carnauba wax. The

resultant granules from each batch were mixed with the equivalence of 3 mg per tablet of magnesium stearate and talc with the addition of the remaining half of maize starch powder as external disintegrant for batches F7-F9. The granules were stored in air-tight containers in preparation for evaluation. Granules required to make 50 tablets per batch was computed and prepared.

2.2.2 Tablet compression

Preliminary testing to determine the most suitable compression pressure was done using a range of pressure from 15-40 KN. After selecting a suitable pressure, batches of the granules were compressed into tablets using a single punch tableting machine (F-3 Manesty Machines, UK) at compression pressure of 32.5KN. The die volume was calibrated to compress tablets of uniform weight by using granules weighing 700 mg. The tablets made were then kept in air tight containers and stored in a desiccator until evaluation.

2.2.3 Evaluation of granules

2.2.3.1 Bulk and tapped densities

A 30 g quantity of the granules was poured gently into a 100 ml graduated measure. The volume of the granules was read and the bulk density calculated. The measure containing the 30 g of the granules was tapped 100 times on a wooden platform. The volume was noted and used in calculating the tapped density. Carr's indices and Hausner's ratios for all the batches of granules were calculated.

2.2.3.2 Flow rate

An Erweka flow tester (Model: GT, GmbH, Germany) was used. The time taken for 20 g of granules to pass through its orifice was recorded. Mean values of triplicate measurements was recorded.

2.2.3.3 Angle of repose

The hollow tube method was used. A short hollow tube of 3 cm in internal diameter sitting on a circular horizontal surface of same diameter was filled with granules. The tube was withdrawn vertically and excess granules allowed to fall off the edge of the circular horizontal surface. The height of the heap was measured. The angle of repose, θ, was calculated using Equation 1.

$$\theta = tan^{-1} (h/r) \quad (1)$$

Where h is the height of the heap of granules and r is the radius of the circular base

2.2.4 Tablet evaluation

The following tests were carried out on the produced tablets and the commercial product; tablet weight uniformity, hardness, friability, disintegration time and dissolution rate, following standard official protocol [12].

Table 1. Formula for preparation of metronidazole granules and tablets

Batch	Metronidazole (mg)	Binders		Disintegrant	Lactose (mg)	Total (mg)
		Carnauba wax (%w/w)	Maize starch mucilage (15 %w/v)	Maize starch (mg)		
FI	600	1	-	-	88	700
F2	600	2.5	-	-	79	700
F3	600	5	-	-	64	700
F4	600	7.5	-	-	49	700
F5	600	10	-	-	34	700
F6	600	15	-	-	4	700
F7	600	1	qs	58	30	700
F8	600	2.5	qs	49	30	700
F9	600	5	qs	34	30	700

qs: quantity sufficient to effectively bind powders

Weight of each of 20 tablets was determined using an electronic balance (College B154, Mettler Toledo, Switzerland) and the mean weight and standard deviation were computed. Ten weighed tablets were placed in the drum of a friabilator (Erweka GmbH, Germany) revolving at 25 rpm which exposed the tablets to rolling and repeated shock resulting from free fall within the apparatus. After 4 min, the tablets were brought out, de-dusted and reweighed. The weight was then recorded and friability calculated as percentage loss in weight.

The crushing strength was determined by diametric compression of each of ten tablets per batch and the commercial product (Campbell Electronics, Model HT-30/50, India). The mean value was calculated.

2.2.4.1 Disintegration time

The disintegration times of six tablets per batch of the formulated tablets and the commercial product were determined in distilled water at 37±0.5℃ using the BP disintegration tester (MK IV, Manesty Machines, UK).

2.2.4.2 Dissolution studies

The dissolution profiles of the optimum batches of the formulated metronidazole tablets and the commercial product were determined using the BP paddle method for the various batches of the tablets (Caleva ST7, UK). A dissolution medium of 900 ml of 0.1 M HCl solution maintained at 37±0.5ºC with a basket revolution of 50 rpm was used. A 5 ml volume of dissolution fluid was withdrawn at various intervals and replaced with an equivalent volume maintained at the same temperature (37±0.5ºC). This was carried out for 120 min. The samples were filtered and diluted appropriately with 0.1 M HCl. The absorbances of the resulting solutions were measured at λmax of 278 nm (T70, PG Instruments Ltd). The concentration and the percentage of drug released at each time interval was determined using the equation from the standard calibration plot obtained from the pure drug. A minimum of triplicate determinations were carried out for all batches and the results were recorded as mean ± SD.

2.2.5 Statistical analysis

Data obtained were computed and analyzed using GraphPad InStat software version 3.10. The statistical difference among batches parameters were obtained using student's t-test at 5 % level of significance.

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Granules properties

The physical properties of the prepared granules are shown in Table 2. Results of the bulk and tapped densities of the batches show an increasing degree of porosity with increasing canauba wax concentrations. The Carr's index values show a trend from the very poor flow character of batches F1 and F2 to the passable and fair flow characters of batches F3-F5, F7 and F8 and the good flow character of batches F6 and F9. Also the Hausner's ratios from the Table show lowest values of 1.15 and 1.17 for batches F6 and F9 with the highest amounts of the wax. The angle of repose values were varied for the batches but less than 30° which implies different degrees of flowability as confirmed by the different flow rate values.

3.1.2 Tablets properties

Table 3 shows the weight variation of the tablets prepared for the various batches of prepared metronidazole tablets. Only two batches (F1 and F2) of the tablets gave an unsatisfactory result for hardness, having values of 1.1 kp each. A minimum crushing strength of 4 kp is desirable for producing tablets with satisfactory characteristics [13]. Table 3 also shows the values of the friability of the tablets. Only batches F7-F9 and the commercial product met the BP specification of less than 1% loss in weight of tablets tested [12].

All the formulated tablets did not disintegrate within 15 min (Table 3) as specified for uncoated tablets [12]. Only the commercial product and batches F7 and F8 met the specification with a disintegration time less than 5 min while batches F1, F2 and F9 disintegrated within 3 h. Batches F3-F6 did not disintegrate at all within 4 h of testing. On the basis of the formulated tablet's crushing strength, friability and disintegration time, three (3) batches (F7-F9) were selected as optimum formulations for the dissolution test.

Table 2. Physical parameters of prepared granules

Batch	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (^{o})	Flow rate (g/s)
F1	0.6061±0.58	0.9091±0.72	33.33±0.81	1.50±0.04	No flow	No flow
F2	0.6061±0.36	0.9091±0.54	33.33±0.61	1.50±0.05	No flow	No flow
F3	0.5714±0.46	0.7692±0.51	19.18±0.31	1.35±0.10	29. 74±0.30	2. 09 ± 0.21
F4	0.5714±0.82	0.7142±0.63	14.70±0.11	1.25±0.22	28. 07±0.51	2. 63 ± 0.22
F5	0.5405±0.25	0.6667±0.84	14.21±0.51	1.23±0.04	27. 76±1.01	2. 92 ± 0.45
F6	0.5263±0.50	0.6061±0.35	13.33±0.01	1.15±0.16	27. 45±0.41	3. 80 ± 0.38
F7	0.5263±0.92	0.6897±0.58	22.06±0.90	1.31±0.08	28. 30±0.61	2. 88 ± 0.10
F8	0.5556±0.72	0.6897±0.92	19.12±0.88	1.24±0.18	25. 97±0.81	3. 55 ± 0.46
F9	0.5714±0.50	0.6667±0.09	13.43±0.11	1.17±0.12	26. 57±0.01	3. 09 ± 0.11

Table 3. Some physicochemical parameters of formulated metronidazole tablets

Batch	Weight variation (%)	Crushing strength (kp)	Friability (%)	Disintegration time (min)
F1	1.96±0.02	1.1±1.23	47.05±2.40	132±1.20
F2	1.90±0.04	1.1±1.41	25.0±1.45	140±1.48
F3	1.10±0.06	5.0±0.95	2.03±1.22	Nil
F4	0.85±0.05	8.4±0.60	1.74±0.99	Nil
F5	1.05±0.04	8.5±1.01	1.49±1.01	Nil
F6	1.25±0.04	10.8±0.85	1.44±1.04	Nil
F7	0.50±0.12	8.08±1.32	0.87±0.15	2.61±0.98
F8	0.65±0.11	8.75±1.22	0.57±0.08	4.86±1.10
F9	0.51±0.01	6.66±0.01	0.29±0.01	178±1.86
CP	0.50±0.01	10.5±0.01	0	3±0.55

CP = Commercial product

Fig. 1 show the release profiles of metronidazole from the selected optimum batches F7-F9 and the commercial product. The dissolution plots of the four samples shows a slower release of the metronidazole from tablets of batch F9 when compared with the release from batches F7, F8 and the commercial product.

3.2 Discussion

From the results obtained, F1 and F2 granules prepared by melt granulation process did not flow due to the small quantity of carnauba wax present resulting in low binding effect on the powder particle. This low binding effect on the particles led to the formation of granules with poor flow properties. The flowability of the granules increased with increased concentrations of carnauba wax as shown in batches F3-F6 due to the increased ability to produce of larger sized granules [14,15] and a more uniform coating of the granules by the wax [16,17]. Unfortunately, when these granules were compressed into tablets, F1-F6 batches still produced tablets with widely varied properties. For example, the tablets crushing strength increased while friability decreased with an increase in the concentration of carnauba wax. Hence, the tablets became less friable on one hand, they equally became very hard on the other hand.

Furthermore, only the very weak and friable tablets produced in batches F1 and F2 disintegrated after over 2 h while the other four batches (F3-F6) did not disintegrate hence warranting the need for a further modification of the formula. Batches F7-F9 were introduced to create balance between friability and hardness and achieve the desired hardness and disintegration properties. This was achieved by introducing additional aqueous binder (15 %w/v maize starch mucilage) in sufficient amount to reduce friability while maize starch powder was added to facilitate disintegration at lower amounts of carnauba wax.

Granules produced by this method were free flowing and met all the flow requirements for good tablets production. Furthermore, tablets of F7-F9 batches had acceptable crushing strength, friability and disintegration time.

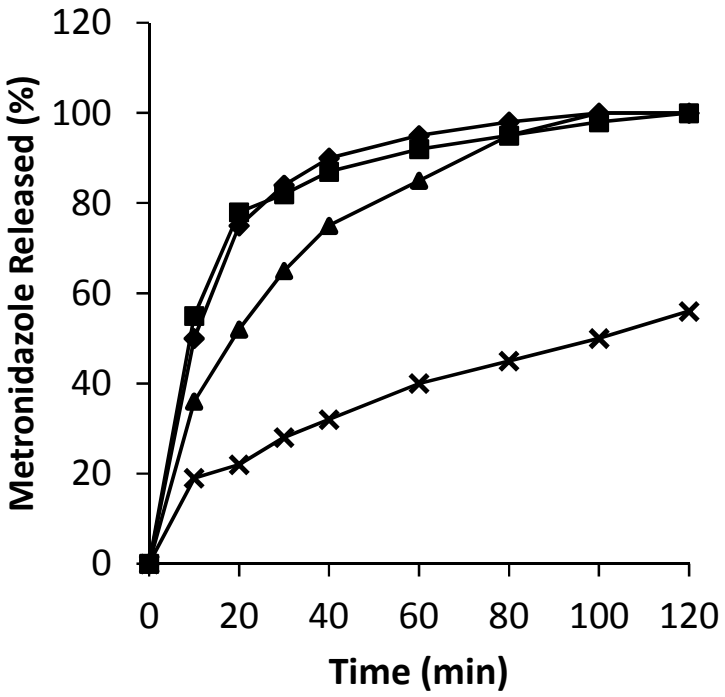

Fig. 1. Dissolution profiles of F7 (◆), F8 (■), F9 (×) and the commercial product (CP) (▲)

In vitro dissolution studies revealed that tablets of batches F7 and F8 still behaved essentially as conventional dosage forms while those of F9 sustained the release of metronidazole with only 60% released over 2 h. This would mean that the carnauba wax coatings of batches F7 and F8 granules used in their tablet production was not sufficient to retard release hence dissolution will be rapid via tablet surface erosion. The release of drug from the F9 batch of tablets was slow due to the formation of a diffusion layer around their tablet forming granules by carnauba wax hence dissolution will more likely be via diffusion through aqueous channels of the tablets [18-20]. The diffusion layer may also hinder influx of the dissolution fluid into the core of the tablet, thus accounting for the greater sustained release of F9 tablets.

It therefore imply that in order to achieve the production of good metronidazole tablets for sustained release using carnauba wax and melt granulation technique, 5% carnauba wax would be considered the optimal amount that may be used for controlled release while the conventional aqueous binder and disintegrant must be included to improve granule and tablet properties.

4. CONCLUSION

The presence of carnauba wax as a polymer binder extended the release profile of metronidazole with formulation F9 releasing 60% of the drug within 2 h and as such it can be used in the formulation of metronidazole sustained release tablet which will enhance patient compliance by reducing the frequency of administration of the drug.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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