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Modification of drug release profile of metronidazole tablet using co-precipitate of irvingia and egg albumin – A proven good technology

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ABSTRACT

This work was aimed at studying the effect co-precipitation of irvingia gum with egg albumin had on the drug release profile of metronidazole tablets. Irvingia gum was extracted from the seed of irvingia gabonensis by maceration method. Some of the irvingia gums were co-precipitated with egg albumin. The irvingia gum (IG) and its co-precipitate with egg albumin (EA) were respectively used as 2% binders to formulate metronidazole tablets. Micromeritics characterization of the granules were performed, afterwhich, they were compressed into tablets. Quality control test such as hardness, friability, disintegration time and dissolution tests were performed on the tablets. The results obtained, showed that flow rate for batch IG was 9.380 g/s and for EA was 3.250 g/s. Angle of repose was 39.860 and 29.680 for batches IG and EA respectively. Compressibility index was 35.330 and 25.470, while Hausner's ratio was 1.550 and 1.342 for IG and EA respectively. Friability was 2.750% and 1.570% and disintegration time was 0.80±0.01 mins and 3.17 ±0.01 min for IG and EA respectively. 50.5% and 19.0% of metronidazole were released after 60 mins from IG and EA respectively. This indicated a marked modification (reduction) in the drug release profile for batch EA.

Keywords: Irvingia Gum, Co – Precipitation, Maceration, Binders, Micromeritics, disintegration time.

INTRODUCTION

Today, the whole world is increasingly interested in natural drugs and excipients. For centuries man has made effective use of materials of natural origin in the medical and pharmaceutical field. Furthermore, they can be modified to obtain tailor made materials for drug delivery systems allowing them to compete with the synthetic products that are commercially available [1]. Natural materials have advantages over synthetic materials because they are non toxic, biodegradable, less expensive and freely available.

Gums and mucilages are typically heterogeneous polyuronides with similar composition which upon hydrolysis, they yield sugars such as arabinose, galactose, glucose, mannose, xylose and various uronic acids [2]. Gums are considered to be pathological products formed following injury to the plant or owing to unfavorable conditions, such as drought, by a breakdown of cell walls (extra cellular formation; gummosis) while, mucilages are generally normal products of metabolism, formed within the cell (intracellular formation) and/or are produced without injury to the plant. Gums readily dissolve in water, whereas, mucilage form slimy masses [1]. Gums are amorphous translucent substances which are insoluble in alcohol and most organic solvents. Gums and mucilages contain hydrophilic molecules, which can combine with water to form viscous solutions or gels. The nature of the compounds involved influences the properties of different gums. Linear polysaccharides occupy more space and are more viscous than highly branched compounds the same molecular weight. The branched compounds form gels more easily and are more stable because extensive interaction along the chains is not possible.[1]

Binders or adhesives are added to tablet formulations to add cohesiveness to powders, providing the necessary bond to form granules which when compressed form tablet. Binders could be natural or synthetic gums. The primary criterion

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when choosing a binder is its compatibility with the other excipients, secondly, it must impact sufficient cohesion to the powder to allow for normal processing and yet allow the tablet to disintegrate and the drug to dissolve upon ingestion, release the active ingredients for absorption.

Irvingia is a genus of African and Southeast Asian trees in the family Irvingiaceae; sometimes known by the common names wild mango, African mango, bush mango, dika or ogbono. They bear edible mango-like fruits, and are especially valued for their fat- and protein-rich nuts. The fruit is a large drupe, with fibrous flesh. The subtly aromatic nuts are typically dried in the sun for preservation, and are sold whole or in powder form. They may be ground to a paste known variously as dika bread or Gabon chocolate. Their high content of mucilage enables them to be used as thickening agents for dishes such as ogbono soup. The nuts may also be pressed for vegetable oil. Its products are of varied pharmaceutical uses and include Dika wax and Dika fat [3]. The mucilage of its kernel has been investigated as a tablet binder, an emulsifying agent and a suspending agent in pharmaceuticals [4,5].

Co-precipitation is the simultaneous precipitation of a soluble component with a macro-component from the same solution by the formation of mixed crystals, by adsorption, occlusion or mechanical entrapment [6]. The aim of co-precipitation, e.g., polymer-polymer interaction, is to produce a stable polymer with better properties than the individual polymers.[7] Co-precipitation which is an example of solid dispersion is a recognized technique for increasing the dissolution of poorly water-soluble drugs so as to improve their bioavailability [8].

A research work carried out to evaluate the suspending properties of the co-precipitate from *Irvingia gabonensis gum variety Excelsa* (Fam: Irvingiaceae) and gelatin, concluded that from the results of the investigation that the suspension prepared with the co-precipitate of *Irvingia gabonensis* gum and gelatin as a suspending agent appears to be superior to those prepared with the gum or gelatin alone as well as a. commercial magnesium trisilicate suspension [9].

A study that was aimed at investigating the effects of *Brachystegia* gum (BG)-egg albumin (EA) mixture as binding agent on the qualities of metronidazole tablets.in which BG and EA were mixed at different ratios to generate fifteen binder mixtures (F1- F15), from which F1-F5, F6-F10 and F11-F15 were used at 2%, 4% and 6% w/w respectively to formulate metronidazole granules by wet granulation, reported that among the metronidazole tablet formulations, those containing binder at 2% w/w released the highest amount of drug, giving up to 90% drug release in 6 h. The least amount of metronidazole was released by tablets formulated with binders at 6% w/w from which only about 30% of drug was released in 6 h. The BG-EA mixture was found useful in imparting slow release profile on metronidazole tablets, which is desirable for some tablet formulations (10). This present work was carried out to study the effect co-precipitation of irvingia gum with egg albumin will have on the drug release profile of metronidazole tablets.

MATERIALS AND METHOD

Materials: Metronidazole (BDH chemical limited Poole England), Lactose (BDH chemical limited Poole England), Magnesium stearate (BDH chemical limited Poole England), Maize starch (BDH chemical limited Poole England), Acetone (BDH chemical limited Poole England), Methanol (BDH chemical limited Poole England), Chloroform (BDH chemical limited Poole England).

Extraction of Irvingia gabonensis (Ogbono gum): *Irvingia gabonensis* seeds were bought from Nsukka, Enugu state and authenticated at Department of Pharmacognosy, Delta State University, Abraka, Delta state, Nigeria. The seeds were dried and ground into powder using a BL 430 series electric blender (Kenwood, UK). The powder was allowed to dry in an oven (DHG-9101.1 SA Ceword medical equipment England) at 60^{o}C.

The powder was defatted by maceration method. 350 g of the dried powder was weighed and soaked in a 1.5 L bottle jar containing 0.9 L chloroform : methanol (2:1) solution. This was thoroughly shaken every hour for 5 hours and it was then allowed to stand. After 24 hours, the filtrate was separated from the residue using a muslin bag. The residue containing Irvingia was dried in the laboratory oven (DHG-9101.1 SA Ceword medical equipment England) at 50^{o} C. The dried powder was soaked with 1.5 L of hot distilled water in a clean bucket. It was allowed to stay for 24 hours and then filtered using a muslin cloth. The mucilage was precipitated with three parts of acetone, i.e 300ml of acetone was added to every 100ml of the solution in the beaker followed by continuous stirring using a spatula until thick mucilage was formed and collected by filtration. The extracted mucilage was dried in the laboratory oven at a temperature of 50^{o} C. The dried mucilage was ground into fine powder using blender. It was then sieved into finer powder using sieve no 100. The sievate was dried further in the oven at a

temperature of 60^{o}C for 60 minutes. It was then transferred into an airtight bottle and stored.

Incorporation of Co-precipitate of Irvingia and Egg albumin: 0.25g of Irvingia gum (standard gum) was placed in a measuring cylinder and 5ml of water was added and stirred in a water bath until mucilage was formed. 0.25g of egg albumin was placed in a measuring cylinder and 5mls of water was added and stirred in a water bath until mucilage was formed. The mucilages were mixed together and stirred to obtain a homogeneous phase and the volume recorded. With glass rod, the mucilage was added to the already mixed excipients until a wet mass was formed. The volume of mucilage used was recorded.

Evaluation of granules: Granules evaluation is important in order to determine the granules properties and its ability to produce good tablets based on their properties.

Flow rate (g/sec): The prepared granules were weighed with JA5003A analytical balance (Falc Instruments srl, Treviglio, Italy) and allowed to flow through a funnel forming a conical pile.

Angle of repose (^{o}): The formulated granules were allowed to flow freely through a funnel. The internal angle between the surface of the pile and the horizontal surface was determined. The height of the conical heap was measured by means of a graduated rule and pins while the diameter/ radius of the granule heap was determined from the circular outlines of the granules heap.

Bulk and Tapped density (g/cm^{2}): 20g of the granules was weighed and poured into a 50 ml measuring cylinder. The surface was levelled and the volume (bulk volume, V_b) recorded. The measuring cylinder was tapped till constant volume (tapped volume, V_t) was achieved and the new volume was recorded.

Carr's index (C.I): This was calculated from the equation below;

$$C.I = \frac{Dt-Db}{Dt} \times 100$$

Where Dt = Tapped density
Db = Bulk density

Hausner's ratio: This was calculated from the equation below;

$$\text{Hausner's ratio} = \frac{Dt}{Db}$$

Where Dt= Tapped density
Db= Bulk density

Formulation of Metronidazole tablets: Two batches of Metronidazole tablets were produced by wet granulation using Irvingia gums and co – precipitate of irvingia gum and egg albumin respectively as binders. Table-1 showed the formula for preparing granules and tablets. The excipients were weighed accurately as provided by the formula to produce 50 tablets. The required quantity of metronidazole, corn starch and lactose were mixed in a mortar. The measured quantity of binder was added and mixed until a damp mass was formed. The damp mass was passed through sieve with mesh size 1.18 mm using a cone spatula and dried at a temperature of 60^{o} C in the laboratory oven. The dried granules were passed through sieve with mesh size 710 μm and dried.

The appropriate quantity of magnesium stearate was added to the fine granules in a powder bottle and tumbled for 2 minutes. The coarse granules were transferred into the mixing bottle and mixed for 5 minutes. The granules were weighed and compressed using a Manesty F3 Single puch tablet Press (Manesty, England) fitted with 10.5 mm biconcave punches at a constant pressure of 2 tons.

Evaluation of Metronidazole tablets

Weight Uniformity: Twenty tablets from the two batches respectively were selected and weighed using electronic balance. The mean and standard deviation for each batch were calculated and the percentage weight variation of 5% for tablet weight more than 250mg was taken as the accepted limit [11].

Hardness test: Ten tablets each from both batches were selected for hardness test. The Monsanto hardness tester (Manesty, England) was used. The tablet to be tested was placed diametrically between the spindle and anvil. Pressure was applied by turning the knob just sufficient to hold the tablet in position. The pointer on the scale was then adjusted to zero. The pressure was then increased as uniformly as possible until the tablet cracked, and the pointer value was read. The force required to break the tablet was measured in kg and the crushing strength of 4kg is usually considered to be the minimum for satisfactory tablet.

Friability test: Erweka friabilator was used for the friability test. Ten tablets each from the batches were dusted, weighed together in a balance and subjected to abrasive shock at 25 rpm for 4 mins in a friabilator.

Disintegration time test: Erweka disintegration unit (Erweka Apparatus, W. Germany) was used for testing the disintegration time of six tablets,

each selected at random from the batches. The six tablets from each batch were placed into each of the baskets in the disintegration test unit respectively. 1000ml of distilled water maintained at $37^{O}C$ was used as the disintegration medium. The individual time taken for all the tablets to break up into small aggregates was recorded in minutes. The average disintegration time for the six tablets was calculated [12].

Dissolution profile studies: The Erweka dissolution apparatus, DT-D model (Erweka Apparatus, W. Germany) filled with 900 ml volume of freshly prepared 0.1N HCl was used. A 5ml sample was withdrawn and replaced immediately with 5ml of fresh 0.1N HCl solution at the same temperature to maintain the total level of the dissolution medium. This was repeated after 10,15,20,25,30,35,40,45,50,55 and 60 mins. The 5ml sample withdrawn, was filtered and the absorbance was taken using Cecil CE 2041 2000 series Ultraviolet spectrophotometer (Cecil instruments, Cambridge, England) at 278nm. The concentrations were calculated using the standard beer Lambert's plot. The percentage release of metronidazole at least 90% of their active constituents [13] were calculated and compared to the standard values in the pharmacopoeia.

RESULTS AND DISCUSSION

Evaluation of granules:

Angle of repose: Different methods of determining angle of repose may produce different values for the same powder due to the difference in the way the samples were handled prior to measurement. Generally powder with angle of repose greater than 40 will have unsatisfactorily flow properties while those with angles close to 25 correspond to very good flow properties. The angle of repose for the granules produced using 2% Irvingia, and co – precipitate of Irvingia and egg albumin binder was 39.86, and 29.68 respectively. This showed that the batch with irvingia showed fair flow while the batch containing irvingia and eggg albumin had an excellent flow properties. This showed that co – precipitation of irvingia with egg albumin improved the flow property of the granules.

Bulk density and tapped density: The bulk densities were 0.540 g/cm^3 and 0.550 g/cm^3 while tapped densities were, 0.835 g/cm^3 and, 0.785 g/cm^3 respectively for the irvingia and co – precipitate of irvingia and egg albumin batches. The bulk and tapped densities of powders and granules provide information on their packing behaviour. It also supplies useful information on tablet porosity, and its' relationship to disintegration time and tablet hardness. Highly irregular particles and larger particles provide less contact between the particles hence creating void spaces and if the void is not filled by smaller particles, a low density will be obtained. The result obtained showed a narrow difference between the bulk density and tapped density of the granules produced by both binders. It can be deduced that the granules were closely packed.

Compressibility index and Hausner's ratio: The compressibility index of the granules containing 2% Irvingia, and Co precipitate of Irvingia and egg albumin were 35.33%, and 25.47% respectively while the Hausner's ratio were 1.550, and 1.342 respectively. Co – precipitation of irvingia with egg albumin resulted in the improvement in flow rate from very poor to passable.

Carr's index and Hausner's ratio are simple, fast, and popular methods of predicting powder flow characteristics. They are one point determinations and do not always reflect the ease or speed with which consolidation of the powders occurs. Some materials have high indices (suggesting poor flow) but they may consolidate rapidly and vice versa. Rapid consolidation is essential for uniform filling on tablet machines.

Tablet evaluation

Weight uniformity: None of the tablets in both batches deviated from the BP specification as shown in table 4. According to BP specification [13] for tablet weighing 250mg and above, not more than two tablets are allowed to deviate from mean by more than 5% to avoid problem of overdosage or underdosage.

Friability test: The friability for the metronidazole tablets formulated with 2% Irvingia and co-precipitate of Irvingia and egg albumin was 2.75 and 1.57 respectively as shown in table 5. The BP specifications [13] stipulates that tablet friability values should not be greater than 1%. This showed that tablets from both batches failed the test but the batch containing co – pre cipitate of irvingia and egg albumin gave a better % friability value. Higher concentration of the binders may be needed to formulate tablets with acceptable friability values.

Hardness test: From the hardness test result on table 6, it can be observed that the hardness values for irvingia tablets ranged from 2.300 to 2.850 ± 0.145 while that of co – precipitate of irvingia and egg albumin ranged from 2.576 to 3.000 ± 0.504. This was below the official stipulated value of not less than $4.000kg/cm^2$(40N). This binder

concemtration (2%) used may be low which resulted in the low crushing strength of the tablet.

Disintegration time: From table 7, the disintegration time for tablets in irvingia batch was 0.80 ± 0.01 mins while that of co = precipitate of irvingia and egg albumin was 3.17 ± 0.01 mins. The BP specifications stipulates that tablet disintegration values should not be more than 15mins, and both batches passed the test.

Dissolution profiles: From tables 8 and 9, and also figure 1, metronidazole tablets formulated with irvingia gum released 39.5% and 50.5 % of metronidazole in 45 mins and 60 mins respectively while metronidazole tablets that were formulated with co – precipitate of irvingia and egg albumin released 16.5% and 19% of metronidazole in 45 and 60 mins respectively. The gum co-precipitated with egg albumin released lower percentage of metronidazole and showed a sustained release profile.

CONCLUSION

Binders or adhesives are added to tablet formulations to add cohesiveness to powders, providing the necessary bond to form granules which when compressed form tablet. It must impact sufficient cohesion to the powder to allow for normal processing and yet allow the tablet to disintegrate and the drug to dissolve upon ingestion, release the active ingredients for absorption. The percentage drug release of metronidazole increased with time for the two batches. The irvingia batch had an acceptable drug release profile but the co-precipitate of irvingia and egg albumin, had a slow and sustained release profile. Dissolution profile and bioavailability studies have shown that formulations that have poor release in vitro often have low bioavailability in clinical studies [14]. Consequently, in vitro dissolution efficiency studies provide valuable information on the release characteristics of solid dosage forms. In vitro dissolution test provide valuable data for the development of pharmaceutical products, an indication of relative potential in vivo performance and means of quality control. This study showed that irvingia gums could be used as a binder in the formulation of metronidsazole tablets. Also, that co – precipitation of the gums with egg albumin could result in alteration of the drug release profile of the tablets from normal to slow or sustained release. Further work should be done using different concentrations of the co – precipitate of irvingia and egg albumin.

Table 1: FLOW PROPERTIES OF GRANULES

FLOW RATE	Angle of repose (^{O})	Carr's index (%)	Hausner's ratio
EXCELLENT	25-30	≤10	1.0-1.11
GOOD	31-35	11-15	1.12-1.18
FAIR	36-40	16-20	1.19-1.25
PASSABLE	41-45	21-25	1.26-1.34
POOR	46-55	26-31	1.35-1.45
VERY POOR	56-65	32-37	1.46-1.59
VERY VERY POOR	≥66	≥38	≥1.60

Table 2: Formula for formulation of metronidazole tablets

Excipients	Quantity per tablet	Quantity for 50 tablets(g)
Metronidazole	0.2g	10
Corn starch	5%	1.25
Binder	2%	0.5
Magnesium stearate	1%	0.25
Lactose	Qs to make up to 0.5g	13

Table 3: Flow properties of Metronidazole granules

BINDER	CONCENTRATION	FLOW RATE (g/s)	ANGLE OF REPOSE (0)	BULK DENSITY (g/cm^3)	TAPPED DENSITY (g/cm^3)	COMPRESSIBILITY INDEX (%)	HAUSNER'S RATIO
IRVINGIA	2%	9.380	39.860	0.540	0.835	35.330	1.550
IRVINGIA AND EGG ALBUMIN	2%	3.250	29.680	0.550	0.738	25.470	1.342

Table 4: Mean and standard deviation on weight uniformity of metronidazole tablets

S/N	IRVINGIA (g)	IRVINGIA + EGG ALBUMIN (g)
MEAN	**0.527 ± 0.003**	**0.525 ± 0.003**
1	**0.003**	**0.003**
2	**0.006**	**0.003**
3	**0.003**	**0.003**
4	**0.003**	**0.002**
5	**0.004**	**0.004**
6	**0.003**	**0.003**
7	**0.002**	**0.002**
8	**0.003**	**0.004**
9	**0.003**	**0.004**
10	**0.001**	**0.003**
11	**0.003**	**0.006**
12	**0.003**	**0.002**
13	**0.002**	**0.004**
14	**0.006**	**0.003**
15	**0.002**	**0.003**
16	**0.003**	**0.002**
17	**0.002**	**0.002**
18	**0.004**	**0.003**
19	**0.002**	**0.003**
20	**0.002**	**0.003**

Table 5: Percentage friability of formulated metronidazole tablet made with 2% binder

S/NO	IRVINGIA	IRVINGIA + EGG ALBUMIN
Initial weight	5.088	5.433
Final weight	4.948	5.348
Weight loss	0.140	0.085
% Weight loss	2.750%	1.570%

Table 6: Mean hardness of formulated metronidazole tablet

S/N	IRVINGIA (± 0.145)	IRVINGIA + EGG ALBUMIN (±0.504)
1	**2.300**	**2.724**
2	**2.850**	**2;846**
3	**2.546**	**2.766**
4	**2.766**	**2.588**
5	**2.589**	**2.934**
6	**2.654**	**2.849**
7	**2.630**	**3.000**
8	**2.540**	**2.997**
9	**2.610**	**2.576**
10	**2.590**	**2.639**

Table 7: Mean disintegration time of formulated metronidazole tablet

S/N	IRVINGIA	IRVINGIA + EGG ALBUMIN
Mean disintegration time	**0.80 ± 0.01**	**3.17 ± 0.01**

Table 8: Dissolution profile of Irvingia gabonensis (2%)

Time (mins)	Absorbance(A)	Density of the drug(mg)	Percentage release
5	0.069	19	9.5
10	0.090	30	15
15	0.110	35	17.5
20	0.120	46	23
25	0.131	52	26
30	0.140	57	28.5
35	0.159	67	33.5
40	0.170	73	36.5
45	0.181	79	39.5
50	0.199	89	44.5
55	0.215	92	46
60	0.221	101	50.5

Table 9: Dissolution profile of irvingia gabonensis and egg albumin (2%)

Time (mins)	Absorbance(A)	Density of the drug(mg)	Percentage release
5	0.069	19	9.5
10	0.075	22	11
15	0.079	24	12
20	0.081	25	12.5
25	0.082	26	13
30	0.086	28	14
35	0.090	30	15
40	0.094	32	16
45	0.095	33	16.5
50	0.099	35	17.5
55	0.100	36	18
60	0.105	38	19

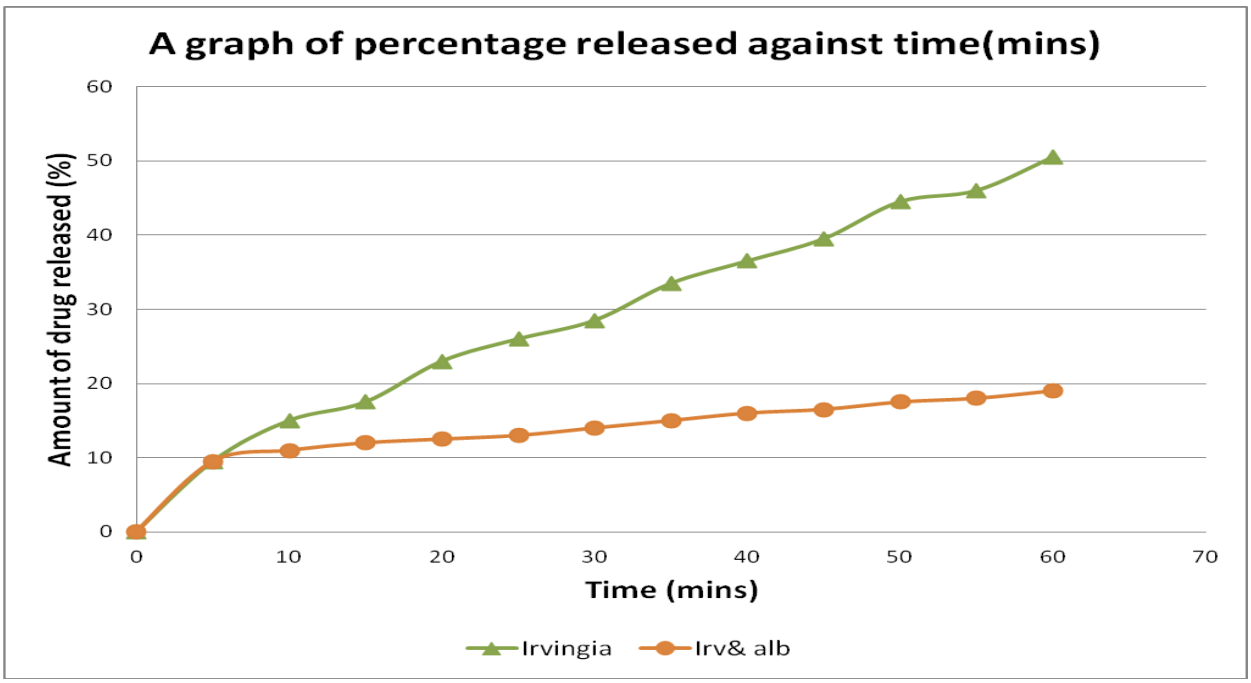

Fig 1: Dissolution profile of metronidazole tablets

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