Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

Formulation and Evaluation of a Solvent Evaporated, Binary-Binder Based Directly Compressible, Excipient "Grewstarag" Granules, and it's Tableting Properties in Ibuprofen and Metronidazole Tablets

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ARTICLE DETAILS

Article history:
Received on 06 October 2015
Modified on 15 November 2015
Accepted on 20 November 2015

Keywords:
Directly compressible excipient,
Coprocessed filler-binder,
Binary-based filler-binder,
Controlled release filler-binder,
Ibuprofen tablets,
Metronidazole tablets

ABSTRACT

A research was carried out to study the effect of increasing concentration of grewia gum in a binary-binder mixture on granules properties of a composite directly compressible excipient made with local primary materials and to formulate Ibuprofen (IBF) and metronidazole (MNZ) tablets with the best granules. This research was designed based on a fixed amount of Nigerian Tapioca Starch (NTS), while varying ratio of grewia gum (GG), and local acacia sieberiana gum (LASG) in the following percentage ratio: 80:0:20, 80:5:15, 80:10:10, 80:15:5, and 80:20:0 respectively. Slurry of physical mixture of GG and LASG was made using mixture of isopropranol and water (2:1) as granulation fluid. Slurry of NTS was also made and was triturated with the binder slurry. The resultant mixture was stirred vigorously until a semi solid mass was formed which was air dried for 72 h. The dried granules were size reduced by passing through 500 µm sieve size. The granules percent(%) cummulative distribution for various batches showed that the batch A with 20 % LASG showed weaker compact granules than every other batch containing binary binder mixture. The granule compactness increases from 20 % LASG and picked at 20 % GG. In between the batches, granules with 10 % GG and 10 % LASG possessed hybrid compactness which was consistent for particles retained on 180 µm, 250 µm and 355 µm. the average granule size was found to greater than 250 µm and less than 355 µm. It was observed that as the proportion of GG increases while LASG decreases, the granules became stronger, flow rate increases, compressibility decreases and viscosity increases. GrewStarag granules containing 80 % NTS, 10 % GG, and 10 % LASG with the following physicochemical properties was chosen: FR, 15.8 g/s; AR, 14.7°; CI, 8.0 %; HR, 1.08; viscosity, 115 mPa.S^{-1}. This was employed for the formulation of IBF and MNZ tablets. The tablet target weight was 505 mg, compressed at 7.5 KN. Evaluation of IBF tablets shows acceptable dilution potential for tablets made with 200 mg of GrewStarag and 300 mg of IBF, having crushing strength (CR), disintegration time (DT), and friability (F) values: 58.2 $\pm$ 2.4 N, 2 h 20 min., and 1.2 % respectively. Evaluation of MNZ tablets revealed acceptable compacts for dilution potential: 300 mg GrewStarag granules and 200 mg MNZ, having CS, 7.0 $\pm$ 1.0 N; DT, 2 h. 21 min., and 1.10 %. GrewStarag, a new filler-binder can be employed to extend or modified the release of moisture sensitive and poorly compressible active pharmaceutical ingredients for non- disintegrating colon targeted drugs.

INTRODUCTION

As a measure to protect most active pharmaceutical ingredients from inactivation by the presence of HCL in the stomach, more effort is needed to design newer non-disintegrating, directly compressible filler binder. Over two decades, several plant gums have been introduced as food additives and pharmaceutical excipients.

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Grewia mollis belongs to the plant genus, *Grewia,* and some authors have classified the genus in the mallow family Malvaceae.

The binding property of grewia gum has been compared with polyvinyl pyrolidone in paracetamol tablet formulations and analysed the compression properties of the formulations using density measurements and application of Heckel and Kawakita equation. The results compares favourably with the PVP. They

concluded that grewia gum could be used as a substitute binder in paracetamol formulations [1].

Grewia gum was reported to possess excellent binding property in sodium salicylate tablets [2]. When used as a binder in concentration range of 2–6% w/w, it was found to be as effective as gelatin and more effective than maize starch or acacia gum. The effect of the method of incorporating the gum into tablet formulation on tablet properties was also reported [3]. They found that tablets with better tablet properties such as hardness and friability were produced when the gum was incorporated by activation with water than by wet granulation or direct compression[3]. In another research it was discovered that acid and thermal treatment of the gum resulted in improved drug release from tablets due to reduction in viscosity of grewia gum [4]. In another development, grewia gum was investigated as a sustained release polymer matrix in ibuprofen [5]. It was used at a concentration of 16%, 32%, and 48% to formulate tablets of ibuprofen. This was compared with similar formulations prepared using hydroxypropyl methylcellulose (HPMC), guar gum, or ethyl cellulose as the polymer matrix. The results concluded that grewia gum at these concentrations could be employed as a sustain release polymer in ibuprofen tablets for up to 24 hours. Tablets of cimetidine containing 40% of grewia gum were prepared by direct compression.

Grewia gum has also been evaluated as a mucoadhesive in tablets [6,7]. In another development, grwia gum compared favourably with tragacanth when used as bioadhesive in tablet formulation [8].

In this research, grewia gum will be used as a binder in various concentrations to augment the binding property of acacia gum in order to modify the functionality of tapioca starch (another plant metabolite used as a bulky excipient) for potential applications in the development of directly compressible, extended release, non-disintegrating tablet.

MATERIAL AND METHODS

Materials

Cassava tuber *(Mannihot esculenta crantz)* obtained from University of Agriculture Abeokuta, Ogun State, Nigeria, *Acacia sieberiana* gum obtained from Jigawa State Ministry Agriculture and Forestry, iodine, Metronidazole, Ibuprofen

Methods

Extraction and Purification of *Acacia sieberiana* gum

The method of Karayya *et al* [9], used by Shittu *et al* [10], was adopted. Five gram (500 g) of the crude gum was dispersed in 1 L of hot distilled water. The hydrocolloid was then filtered through 75 µm size linen. The gum was precipitated from the aqueous, medium by adding slowly while stirring, 5 L of 95 % ethanol. The gum was dried in a Gallenkamp oven (model BS) at 60°C.

Extraction of Tapioca Starch

Cassava tubers were washed and peeled to remove the outer skin and rind with the aid of a handy stainless knife. The peeled tubers were washed with freshly distilled water and rasped. The rasp consists of a sheet of metal plate perforated with nails, clamped around a stainless bucket with the protrusions facing outwards. The tubers were then manually rasped to a pulp on the stationary grater (which is the metal plate perforated by nails). Water was applied in small quantities continuously to the rasper. The process was continued until the whole tubers were turned into a fine pulp in which most but not all of the starch granules were released.

After rasping, pulp from the sump was then pumped on to a nylon fastened /clamped around a stainless bucket. A small spray of water was applied to assist the separation of starch granules from their fibrous matrix and to keep the screen mesh clean while water was added, the mass were turned manually to aid the release of the granules. Starch granules carried with the water fall to the bottom of the bucket in which the sieve was placed. The starch milk was then allowed to sediment, by standing for a period of 8 h. The starch settled at the bottom of the bucket and the supernatant liquor decanted. The sediment / fine granules were centrifuged. After the removal of free water from the starch, cake was obtained. The starch cake was then crumbled into small lumps (1-3 cm) and spread out in thin layers on stainless trays and air dried for 120 h [11].

The slurry form of tapioca starch (NTS) (sieved fraction, <75 µm) was coprocessed with a mixture of native acacia sieberiana gum (LASG), and grewia gum (GG) (sieved fraction, <75 µm) using the method of Tsai *et al* [12].

Table 1: Formula for Formation of Grewstarag

	BATCH				
Material	**B_1**	**B_2**	**B_3**	**B_4**	**B_5**
Tapioca starch (TS) (%)	80	80	80	80	80
Grewa gum (GG) (%)	0	5	10	15	20
Acacia gum (AG) (%)	20	15	10	5	0

Solvent used: Isopropanol and water (2:1)

Table 2: Content of 500 mg Grewstarag Granules

	BATCH				
Material	B_1	B_2	B_3	B_4	B_5
Tapioca starch (TS) (mg/tab)	300	300	300	300	300
Grewa gum (GG) (mg/tab)	0	50	100	150	200
Acacia gum (AG) Mg/tab)	200	150	100	50	0

The slurry was made by suspending the NTS in a solution of Isopropranol and freshly distilled water in ratio 2:1 respectively. NTS slurry was blended with the slurry of LASG and GG mixture at concentrations indicated in Table 1, as a dried mass relative to NTS. The composite slurry was stirred vigorously with a stirrer until a semi-solid mass easily ball was formed. The composite mass was then granulated through a 1500 µm and codried at 60^{o}C until a constant weight was reached. Codried granules were pulverized and sized by passing through mesh size 500 µm. The powder and tabletting properties of the codried products were evaluated.

Table 3: Formula for Formulation of Tablets

Ingredients	Quantity
GREWTARAG + IBF	500 mg
Mg Stearate (0.5 % w/w)	2.5 mg
Talc (0.5 % w/w)	2.5 mg
Tablet Weight	505 mg

COMPACTION

The various batches of coprocessed filler binders,"Grewstarag" (Table 1) were compressed on a single punch Erweka tabletting machine (Erweka, AR 400. Germany), fitted with 10.5 mm diameter flat faced punch and die. Tablet target weight was 505 mg (Table 2), and pressure load used was 7.5 KN.

Moisture content

The moisture content (MC) of the granules were determined by weighing 100 g of the powder after which it was heated in an oven at a temperature of 105 °C until a constant weight was obtained.

The moisture content was then calculated with the following formula:

$$MC = (1 - W_t/W_0) \text{ X } 100 \text{ ..... } (1)$$

Where W_t and W_0 represent weight of powder after time 't' and the initial weight before heating respectively.

Determination of Flow Rate and Angle of Repose

Angle of repose was determined using a standard method and equation 3 bellow.

$$\theta = \tan'^{1} (h/r) \text{ ..... } (2)$$

The flow rates were determined with the aid of Erweka flowability tester (model GDT, Germany).

Densities

Bulk and Tap density

These parameters were determined by weighing 50 g quantity of each granule/powder and pouring into a 100 ml measuring cylinder. The volume (V_o) was recorded as the bulk volume. The total weight of the granule/powder was noted. The bottom of the cylinder was raised 10 cm above the slab and made to fall on the platform continuously for 100 taps. The volume of (V_t) of the granule was recorded, and this

represents the volume of the granules minus the voids and is called the tapped volume. The final weight of the powder too was recorded as the tapped weight.

The bulk and tapped densities were calculated as:

$$B_d = W/V_o \quad \ldots\ldots\ldots (3)$$
$$B_t = W/V_t \quad \ldots\ldots\ldots (4)$$

Where, B_d and B_t, are bulk and tapped density respectively, and W, is the weight of the powder (50 g).

The results presented are the mean of three determinations.

Carr's Index

$$\text{Carr's Index (CI)} = (\rho^T - \rho^o)/\rho^o \times 100\ \% \quad \ldots\ldots\ldots (5)$$

Where ρ^o is the poured or bulk density and ρ^k is the tapped density.

Evaluation of Tablets [13-15]

Weight variation Limit Test: The weights of 10 tablets were determined individually and collectively on a Metler balance (Denver, XP-300, U.S.A). The mean weight, percentage (%) deviation from the mean and standard deviation were calculated.

Thickness of Tablets

The thickness of the tablets was measured with the aid of micrometer screw gauge. Five tablets were selected randomly and the thickness for each was measured and the mean value determined.

Hardness of tablets

Crushing strength was determined using an electronic/digitalized tablet hardness tester (model EH O1, capcity 500 N, Indian).

Friability

The friability test was performed for the tablets formulated in a friabilator (Erweka, TA 3R). The weight of 10 tablets was determined on a Metler balance (Denver, XP - 300, U.S. A). The tablets were placed in the friability and set to rotate at 25 r.p.m for 4 min after which the tablets were de-dusted gently and their weight determined. The difference was calculated and the percentage loss in weight and hence the value of the friability was calculated.

Compact Volume: The volume of a cylindrical tablet having radius 'r' and height 'h' is given by the following equation:

$$Vc = h\pi r^2 \quad \ldots\ldots\ldots (6)$$

Compact density: The compact density of a tablet was calculated from the following equation:

$$\text{Compact density } (\rho) = \frac{\text{Weight of tablet}}{\text{Volume of tablet}} \quad \ldots (7)$$

Compact Radial tensile strength

The tensile strength of the normal tablets (T) was determined at room temperature by diametral compression[21] using a hardness tester (model EH O1, capacity 500 N, Indian) and by applying the equation:

$$T = 2\ F / (\pi dt) \quad \ldots\ldots\ldots (8)$$

Where T is the tensile strength of the tablet (MNm^{-2}), F is the load (MN) needed to cause fracture, d is the tablet diameter (m). Results were taken from tablets which split cleanly into two halves without any lamination. All measurements were made in triplicate, and the results given are the means of several determinations.

Compression pressure: This was derived from the relationship between the applied pressure and surface area.

$$\text{C.P.} = \frac{\text{Applied force}}{\text{Surface area of tablet}} \quad \ldots\ldots\ldots (9)$$

Disintegration Time

Disntegration apparatus (Erweka, ZT 3, Germany) was employed. Three tablets were placed in each compartment of the disintegration basket which was lowered into a glass beaker (1 L capacity) filled with deionized water to 800 ml mark and in turn was placed in a water bath maintained at 37 ^oC. The time taken for the disassociated tablet particles to pass through the mesh was recorded as the disintegration time. Average of three readings was taken as the disintegration time.

Determination of dilution capacity

Ibuprofen and metronidazole were used as model drugs /active ingredients.

Model drug was blended in deferent ratios, ranging from 0 %, 5 %, 10 %, up to 50 % with the new composite filler binder.

Formulations were blended by method of dilution and lubricated with 1 % magnessium stearate. Each batch was compressed for 30 seconds on single punch Carver hydraulic hand press(model, C, Carver Inc. Menomonee Falls, Wisconsin, U.S.A) at pressure load of 7.5 KN, target weight of 500 mg. Compacts were allowed to relax for 24 h post compression. Compact dimensions (diameter and thickness) were determined using a digitalized vernial caliper. Crushing strength was determined using an electronic/digitalized tablet hardness tester (model EH O1, capcity 500 N,Indian).

In general, the capacity was expressed by the dilution potential as being an indication of the maximum amount of active pharmaceutical ingredient that can be compressed with the excipient, while still obtaining tablets of acceptable quality.

RESULTS AND DISCUSSION

This research was designed based on a fixed amount of Nigerian Tapioca Starch (NTS), while varying ratio of grewia gum (GG), and local acacia gum (LAG) in the following percentage ratio: 80:0:20, 80:5:15, 80:10:10, 80:15:5, and 80:20:0 respectively (Table 1 & 2).

The granules percent (%) cumulative distribution for various batches showed that the batch A with 20 % LAG showed weaker compact granules than every other batch containing binary binder mixture. The granule compactness increases from 20 % LAG and picked at 20 % GG. In between the batches, granules with 10 % GG and 10 % LAG possessed hybrid compactness which were consistent for particles retained on 180 µm, 250 µm and 355 µm (Fig.1).

The average granule size was found to greater than 250 µm and less than 355 µm. It was observed that as the proportion of GG increases while LAG decreases, the granules became stronger, flow rate increases, compressibility decreases and viscosity increases.

Batch C (comprising of NTS, 80 %; GG, 10 %; and LAG, 10 %) was employed for the formulation of IBF and MNZ tablets. The tablet target weight was 500 mg, compressed at 7.5 KN. The component of the formulation was reflected in Table 3.

Table 4, shows the results of physicochemical properties of individual primary excipient (GG, AG, and TS). The results reflect poor characteristic properties of individual material in terms of flow, compressibility.

Table 5 shows the physicochemical properties of various composite granules in batches. There were great improved flow and compressibility of the composites for all batches over the primary excipients.

GrewStarag granules containing 80 % NTS, 10 % GG, and 10 % LAG with the following physicochemical properties was chosen: FR, 15.8 g/s; AR, 14.7^{o}; CI,8.0 %; HR, 1.08; viscosity, 115 mPa.S^{-1} (Table 5).

Evaluation of IBF tablets shows acceptable dilution potential for tablets made with 200 mg of GrewStarag and 300 mg of IBF, having crushing strength (CR), disintegration time (DT), and friability (F) values: 58.2 $\pm$ 2.4 N, 2 h 20 min., and 1.2 % respectively (Table 6).

Evaluation of MNZ tablets revealed acceptable compacts for dilution potential: 300 mg GrewStarag granules and 200 mg MNZ, having CS, 7.0 $\pm$ 1.0 N; DT, and 1.10 % (Table 7).

The compacts of metronidazole are stronger and can withstand hazard of handling and transportation mire than those of ibuprofen. This can be explained on the ground of bond formation between the components of the filler binder on one hand, and, filler binder and the active ingredient on the other hand. The strength of a tablet is determined by the sum total of bonds formed within the tablet.

SUMMARY AND CONCLUSION

GrewStarag, batch C containing: NTS, 80 %, GG, 10 % and LAG, 10 %, a new filler-binder can be employed to formulate a non-disintegrating extended release tablets of moisture sensitive and poorly compressible active pharmaceutical ingredients. It can be employed for the formulation of matrix tablet of Ibuprofen and colon targeted drug release.

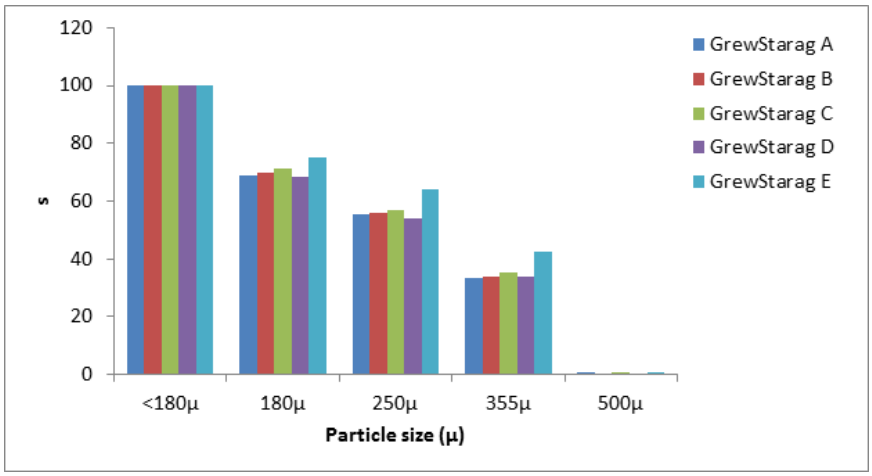

Figure 1: Granule size distribution (µm) *vs* Cummulative retained oversize (%) [GrewStarag]

Table 4: Physicochemical Properties of Grewia Gum, Acacia Sieberiana Gum and Tapioca Starch Granules

Material	Flow Rate (g/sec)	Angle of Repose (o)	Bulk density (g/cm³)	Tapped density (g/cm³)	Compressibility index (%)	Hausner's ratio
Grewa gum (GG)	2.76±	39.3±	0.445	0.601	26	1.35
Acacia gum (AG)	7.36±	32.8±	0.837	0.930	10.0	1.11
Tapioca starch (TS)	2.0±0.02	43.4±0.0	0.545	0.817	33.2 %	1.5

Table 5: Physicomechanical Properties of Various Batches of Composite filler-binder "Grewstarag" Granules

Material GREWS-TARAG (%)	**Batch**	**Flow Rate (g/sec) n=3**	**Angle of Repose (o) n=3**	**Bulk density (g/cm³)**	**Tapped density (g/cm³)**	**Compre-ssibility index (%)**	**Hausner's ratio**	**Moisture Content (%) n=3**	**pH at 25°C**	**Viscosity (mPa.S-1)**
80:0:20	B1	15.1± 0.5	15.6± 0.2	0.663	0.691	4.10	1.04	7.94± 0.12	6.83	50.00± 10.00
80:5 :15	B2	13.8± 0.2	15.3± 0.1	0.673	0.740	9.10	1.10	7.30± 0.20	6.78	75.00± 5.00
80:10:10	B3	15.8± 0.4	14.7± 0.3	0.672	0.730	8.00	1.08	7.90± 0.10	6.77	115.00± 5.00
80:15:5	B4	17.1± 0.1	16.3± 0.1	0.613	0.659	6.98	1.07	7.38± 0.12	6.75	163.00± 5.50
80:20:0	B5	20.7± 0.3	20.7± 0.3	0.688	0.748	8.02	1.09	7.38± 0.20	6.74	200.00± 5.00

Table 6: Compact Properties of GREWSTARAG-IBUPROFEN Compressed Tablets

Batch	**DCE/AI [IBF] (mg)**	**Tab wt. (g) n=3**	**Tab Thickness (cm) n=3**	**Tab Hardness (N) n=3**	**Tab Volume (cm³)**	**Tab Density (g/cm³)**	**Friability (%)**	**Disintegration Time (min) n=3**
A	100+400	0.501±0.01	4.69±0.10	41.8±0.4	0.406	1.234	1.9	52±2
B	150+350	0.497±0.05	4.72±0.05	49.2±0.5	0.408	1.224	1.7	95±1
C	200+300	0.500±0.02	4.80±0.05	58.2±0.6	0.415	1.204	1.2	140±2
D	250+250	0.492±0.10	4.84±0.02	57.1±0.4	0.419	1.176	1.2	154±2
E	300+200	0.495±0.10	4.90±0.05	55.7±0.3	0.424	1.167	1.0	171±2

DCE and AI denotes: directly compressible excipient and active ingredient, respectively
Compression Pressure 7.5 KN. Punch/Die Diameter, 10.5 Mm

Table 7: Compact Properties of GREWSTARAG-METRONDAZOLE Compressed

Batch	DCE/AI [MNZ] (mg)	Tab wt. (g)	Tab Thickness x 10^{-1}(cm)	Tab Hardness (N)	Tab Volume (cm^3)	Tab Density (g/cm^3)	Friability (%)	Disintegration Time (min)
A	100+400	-						
B	150+350	0.505±0.05	4.63±0.01	4.3±0.5	0.400	1.263	2.5	78±3
C	200+300	0.497±0.03	4.39±0.01	5.1±1	0.389	1.277	2.0	75±5
D	**250+250**	**0.497±0.06**	**4.33±0.05**	**5.4±1**	**0.383**	**1.282**	**1.2**	**82±2**
E	300+200	0.481±0.15	4.39±0.01	7.0±2	0.389	1.237	1.1	141±1

Compression Pressure 7.5 KN. Punch/Die Diameter, 10.5 Mm. DCE and AI denotes: directly compressible excipient and active ingredient, respectively.

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