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Physicochemical Characterization of a Co-Processed Excipient (*Gelactomucin*) With Cellactose and Alpha-Anhydrous Lactose

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ABSTRACT

Excipients in recent times have been conferred with improved functionalities through chemical, physical modification and co-processing. This study was aimed at preparing Gelactomucin, a co-processed excipient using co-fusion method, and evaluating its physico-chemical properties comparatively with Cellactose – 80 and Alpha-anhydrous lactose. The parameters investigated were swelling capacity, loss on drying, moisture content, bulk and tapped densities, angle of repose and true density. The results obtained for the co-processed excipient were swelling capacity 104 %, loss on drying 1.7% and angle of repose 25^0. Cellactose-80 recorded 128 %, 1.4 %, 19 ^{O} for swelling capacity, loss on drying and angle of repose respectively. The comparison showed that *Gelactomucin* could compete favourably with the reference excipients.

Keywords: Excipient, Physico-chemical properties, co-processing.

INTRODUCTION

In recent times, improved functionalities have been conferred on excipients through chemical, physical modification and co-processing (Casalderry, *et al.,* 2004). Co-processing seems to be an interesting method because the products are in a special way physically modified without losing their chemical structure and stability (Nachaegari and Bansal, 2004). Powder flow has been shown to depend on size, size distribution or shape of the powder particles and is influenced by physical rather than chemical properties (Thalberg, *et al.,* 2006). Direct compression has been the main-stay method of tableting due to its few processing steps, elimination of heat and moisture, simplified validation, improved drug stability compared to wet granulation technique as well as being economical (Mohammed *et al.,* 2009).

The physico-mechanical properties of excipients that ensure a robust and successful process are good flowability, good compressibility, low lubricant sensitivity, low or no moisture sensitivity etc. (Armstrong and Palfrey, 1989). A good filler-binder is expected to possess good compactibility, dilution potential and sensitivity against lubrication (Sameh *et al.,* 2011). This study determined and evaluated the properties of a three-component co-processed excipient produced from optimized ratios of lactose, mucin and gelatin in comparison with standards like cellactose and alpha-anhydrous lactose and related these properties to their performance in terms of flow and consolidation using the density measurements as assessment parameters.

MATERIALS AND METHODS

Gelatin, Acetone, Lactose, (Sigma-Aldrich, Chemic GmbH, Germany), Cellactose, Alpha- anhydrous lactose (Ausmasco Pharma Co. Ltd., China).

Extraction of mucin: The extraction of bovine mucin was carried out as described by Momoh *et al.,* 2012. The small intestines of the freshly slaughtered cow were obtained from the Zango - Zaria abattoir, Nigeria and dissected starting from the beginning of the jejunum to the ileocaecal sphincter.The intestines sectioned into short lengths was flushed through with chilled saline and the mucosal surface was exposed by longitudinal dissection. Using a microscope slide, the mucus layer was gently scrapped off into the chilled saline. The mucus was precipitated using chilled acetone and dried (lyophilized). The resultant flakes were pulverized using a milling machine and stored in an air-tight container until used.

Preparation of the co-processed excipient

Lactose, mucin and gelatin in the ratio 90:1:9 were fused together by dispersing them in distilled water already heated in a water bath to 400C as described by Adeoye and Alebiowu, (2014).

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The dispersion was then stirred for 15min at the same temperature to form a paste. The resulting paste was then dried at 40^0C in a hot air oven for 2h before screening with a 1.5mm sieve, finally dried for 10min then passed through a 500µm sieve and stored in a screw-capped bottle.

Scanning electron microscopy (SEM)

The morphology of the samples was observed using Scanning Electron Microscopy. The sample was coated under argon atmosphere with gold/palladium and examined under the scanning electron microscope (Phenom World, Einedhoven, Netherlands).

Swelling Capacity (S)

The method of Ohwoavworhua and Adelakun (2005) was used. 1.0g each of the sample was placed in each 15ml plastic centrifuge tubes and the volume occupied was noted. 10ml of distilled water was added from a 10ml measuring cylinder and stoppered.

The contents were mixed in a vortex mixer (Vortex Gennie Scientific, USA) for 2 min. The mixture was allowed to stand for 10min and immediately centrifuged at 1000 rpm for 10min. the supernatant was carefully decanted and the volume of sediment measured. The swelling capacity was computed using the equation.

$$S = \frac{V_2}{V_1} \quad \text{..... (i)}$$

Where S = swelling index

V_1 = volume occupied by the powder prior to hydration

V_2 = volume occupied by the powder after hydration

Loss on drying

The method adopted was a modification of that specified in the USP/NF (2005). A 1.0g quantity of the sample was transferred into a petridish and then dried in an oven at 105^0C until a constant weight was obtained. The % moisture content was then determined as the ratio of the weight of moisture loss to weight of sample expressed as %.

pH determination

This was done by shaking a $1\%^{w}/_{v}$ dispersion of the sample in water for 5 min and the pH determined using a pH meter (Corning, model 10 England) (Emeje *et al.,* 2009).

Angle of repose

The static angle of repose θ was measured according to the fixed funnel and free standing cone method (Ohwoavworhua and Adelakun, 2005). A funnel was clamped with its tip 2cm above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The heights (b) of the powder cones and the mean diameters (D) of the base of powder cones were determined and the tangent of the angle of repose calculated using the equation:

$\text{Tan } \theta = 2h/D$ ..... (ii)

Bulk and tapped densities

A 2.0g quantity each of the powder sample was placed in a 10ml measuring cylinder and the volume, V_0 occupied by each of the samples without tapping was noted. After 100 taps on the table, the occupied volume V_{100} was read. The bulk and tapped densities were calculated as the ratio of the weight to volume (V_0 and V_{100} respectively).

Compressibility Index

This was calculated using the equation:

$$\text{Compressibility Index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100 \quad \text{.....(iii)}$$

Hausner's ratio: This was calculated as the ratio of tapped density to bulk density of the samples.

Porosity

Porosity was calculated based on the apparent density and the true density of the powders where apparent density is the mass of a powder divided by its apparent volume and true density is the mass of a powder divided by its volume, excluding open and closed pores. Porosity (ε) was calculated based on the mathematical equation.

$$\varepsilon = 1 - \frac{\text{Apparent density}}{\text{True density}} \quad \text{..... (iv)}$$

RESULTS

Table 1 gives us the result of the quantitative analysis from the scanning electron microscopy of the various excipients. The co-processed excipient was seen to have the highest mean equivalent diameter. Results in Table 2 show some of the physico-chemical parameters of test and reference co-processed excipients. The swelling characteristics of the three excipients was studied. The result showed that Cellactose – 80 had high swelling index (128%) suggesting that it may perform well as binder/disintegrant. This of course should be as a result of cellulose present in the combination (Armstrong *et al,* 1996; Luiz *et al.,* 2005).

Table 1: Quantitative analysis of excipients

Excipient	Mean equivalent diameter (µm)	Aspect ratio
Lactose	34.1	0.63
Mucin	41.7	0.60
Gelatin	34.9	0.64
Co-processed excipient	79.6	0.62
Physical mix	52.0	0.69

Table 2: Some physicochemical characterization of Co-processed excipient (*Gelactomucin*, Cellactose and Alpha-anhydrous Lactose)

Parameters		Results (SD)
Gelactomucin		
Swelling capacity (%) in water		104%
Loss on drying		1.7%
True density (g/cc)		1.37 (0.04)
Density of powder	Bulk density (g/cc)	0.55 (0.02)
	Tapped density (g/cc)	0.66 (0.01)
Compressibility index		17.37%
Hausner's quotient		1.2
Angle of repose		25^0 (0.55)
Flow rate (g/sec)		6.23
pH		6.99
Cellactose – 80		
Swelling capacity (%) in water		128%
Loss on drying		1.4%
True density (gcc)		1.54 (0.08)
Density of powder	Bulk density (g/cc)	0.43 (0.0)
	Tapped density (g/cc)	0.53 (0.0)
Compressibility index		18.87%
Hausner's quotient		1.2
Angle of repose		19^0 (0.57)
Flow rate (g/sec)		4.65
pH		7.11
Alpha-anhydrous Lactose		
Swelling capacity (%) in water		103%
Loss on drying		1.1%
True density (g/cc)		1.5 (1.06)
Density of powder	Bulk density (g/cc)	0.5 (0.0)
	Tapped density (g/cc)	0.77 (0.09)
Compressibility index		34.67%
Hausner's quotient		1.5
Angle of repose		48^0 (1.06)
Flow rate (g/sec)		1.18
pH		7.11

DISCUSSION

From the result of the quantitative analysis on the scanning electron microscopy of the various excipients, the co-processed excipient was seen to have the highest mean equivalent diameter revealing an increase in particle size as a result of particle engineering. This is in consonance with the work of Ogunjimi and Alebiowu, (2013). Plate 1 further agrees with the outcome of Table 1 where there was agglomeration of the particles as well as increase in the particle size of the co-processed excipient compared to that of the physical mix. This is due to the synergistic effect of the various components and interaction at sub-particle level thereby resulting in larger particles and improved flow as opined by Mullarney et al., (2003) and Dare et al., (2006).

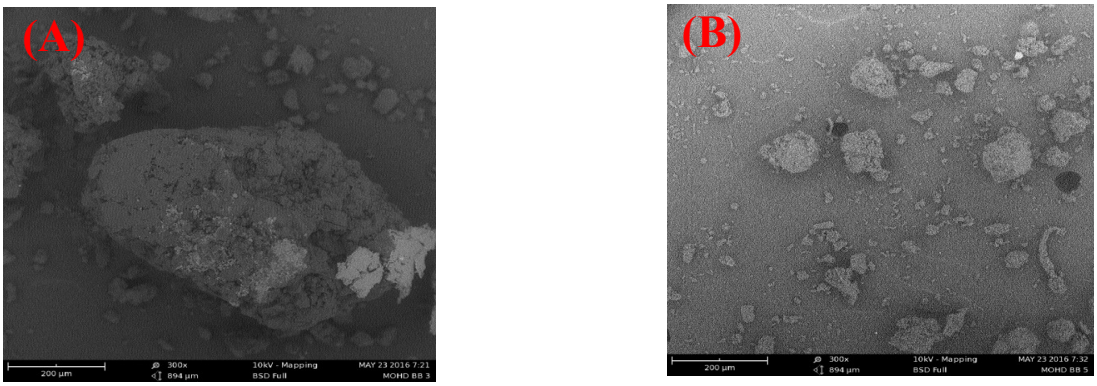

Plate I: SEM Photomicrographs (300X) of (A) Co-processed excipient and (B) Physical mix of excipients

The presence of cellulose fibres in the macroporous particles provides good disintegration properties to Cellactose (Garr and Rubinstein, 1991). The swelling index is in the order Cellatose – 80 > Gelactomucin > Alpha- anhydrous lactose. The moisture content of Alpha-anhydrous lactose was the lowest, suggesting it is very suitable for moisture sensitive drugs. It's in the order Alpha-anhydrous lactose < Cellactose < Gelactomucin. All the three fall below 2% but above 1%. Given suitable temperature, moisture will lead to the activation of enzymes and proliferation of micro-organisms, this in turn will lead to reduction in the shelf life due to instability problems.

It is therefore important to investigate for the moisture content of a material because the economic importance of an excipient for industrial application lies not only on the cheap and ready availability of the biomaterial but by the optimization of production processes such as drying, packaging and storage (Krycer *et al.,* 1982; Sonnergaard, 1999). It is very important to note the pH of an excipent while determining its suitability in formulation since stability and physiological activity of most preparations depend on pH (Liuz *et al.* 2005). The pH for the three excipients were neutral and tending more to basic pH, which implies that when used in uncoated tablets, it may not cause gastric irritation and they can also be useful in the formulation of acidic drugs (Emeje *et al.,* 2009).

The density and flow properties of the test and reference excipients are shown in Table 2. The Hausner's ratio, Carr's index, angle of repose, flow rate were used to assess the flow properties of the excipients. The angle of repose (θ) gives an indication of its inter-particulate frictional forces operating within the powder system by quantifying the resistance of the powder mass to flow (Staniforth and Aulton, 2007). Values of θ less than 25^{o} is indicative of fair to good powder flow, while values greater than about 40^{0} suggest that the material has very poor flow. Generally, values below about 30^{0} range are considered to be appropriate for solid dosage form technology (Zhou *et al,* 2010).

From the result, on Table 2, cellactose (19^{0}) and *gelactomucin* (25^{0}) both had very good flow compared to alpha-anhydrous lactose (48^{0}) that had very poor flow. A hausner's ratio of 1.2 and below is indicative of good flowability while values of 1.5 and above suggest poor flowability.

This result however corresponds with the result obtained for the angles of repose. *Gelactomucin* and cellactose both had a HR of 1.2 while AAL had 1.5 which suggests poor flowability (Adeoye and Alebiowu, 2014). The flow rate is another parameter used in determining the flow behaviour of an excipient. It is in the order *Gelatomucin* > Cellactose – 80 > Alpha-anhydrous lactose. However, Alpha-anhydrous lactose has better fluidity than native lactose though the compressibility is borderline but it has relatively poor dilution potential (Nachaegari and Bansal, 2004).

For compressibility index, values below 15% usually give rise to good flow characteristics, but readings above 25% indicate poor flowability. This revealed that *Gelactomucin* which is the test excipient (17.37%) performed far better than Cellactose (18.87%) but much better than Alpha-anhydrous lactose (34.67%) which was above 25% (Gohel *et al.,* 2007). This corroborates the results of other flow

characteristics. The poor flow exhibited by alpha-anhydrous lactose may be as a result of the moisture content falling below 3% level (1.1%) which leads to a loss of some of the material's direct compression properties (Flores *et al.,* 2000).

CONCLUSION

The results obtained from this work showed that co-processing lactose with gelatin and mucin would enhance packing and flow properties of the excipient produced. Scanning electron microscopy showed that co-processing of excipients led to increased particle size compared to the physical mix. Also, the co-processed excipient (*Gelactomucin*) competed favourably with other modified standard excipients like Cellactose – 80 and Alpha-anhydrous lactose.
On account of these, *Gelactomucin* may therefore be a useful filler-binder in tablet formulations.

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