Formulation and Evaluation of Novel Coprocessed Excipients of Maize Starch and Acacia Gum (*StarAc*) For Direct Compression Tabletting

A.K Olowosulu[1]*, Avosuahi Oyi[1], A.B. Isah[1], M.A. Ibrahim[2]

[1]Department of Pharmaceutics and Pharmaceutical Microbiology, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Nigeria

[2]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, University of Jos, Jos, Nigeria

Abstract

The objective of this work was to develop an efficient direct compression tabletting excipient of coprocessed particles of maize starch (MS) and acacia gum (Ac) by co-drying their well dispersed aqueous mixtures. Weighed quantities of MS and Ac in various mixing ratios of 97.5:2.5, 95:5, 92.5:7.5 and 90:10 were used to form the coprocessed excipients (StarAc). Two forms of the StarAc were produced using fully and partially pregelatinization methods. The StarAc thus produced were evaluated for powder properties namely, bulk and tapped density, angle of repose, flow rate, Carr's index and Hausner's ratio. Tabletting properties namely; weight variation, thickness and diameter, crushing strength, friability and disintegration time of placebo tablets produced with StarAcs were also evaluated. The results of physical properties evaluation revealed that the various coprocessed excipients (StarAc) have good flowability. The fully pregelatinized form of StarAc showed superior flowability when compared with the partially pregelatinized form. However, the results of tablet properties of placebo tablets made using StarAc showed that tablets made using the partial pregelatinization method had good crushing strength/friability profile and acceptable tablet disintegration time. In contrast, tablets produced using fully pregelatinized method did not produce tablets with acceptable quality in terms of strength and friability. Therefore, the partially pregelatinization method was chosen as the preffered method of coprocessing maize starch and acacia. Partially pregelatinized coprocessed excipients of MS and Ac could be developed for use in direct compression tabletting.

Keywords: Co-processed excipients, Maize starch, Acacia gum, StarAc, pregelatinization direct compression, tablets.

INTRODUCTION

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared by either compression or moulding methods[1]. The tablet is still the most frequently administered dosage form for medical applications[2]. Tablets are manufactured by mainly three techniques: wet granulation, dry granulation and direct compression. In wet granulation and dry granulation techniques, various processing steps and manufacturing challenges are involved, leading to higher cost and time of tablet production. In contrast to this, the direct compression technique involves simply the compression of dry blend of powders that comprises the drug and various excipients. The simplicity and cost-effectiveness of the direct compression process have positioned it as a preffered alternative[3].

A wide range of materials from various sources have been developed and marketed as directly compressible vehicles such as lactose, starch, cellulose derivatives, inorganic substances, polyalcohol, and sugar-based materials. Furthermore, many grades of existing excipients such as spray dried lactose, microcrystalline cellulose (MCC), granular dicalcium phosphate, crospovidone and pregelatinized starch have been introduced in the market but performance improvement was achieved only up to a limited extent[4]. In addition to development of directly compressible excipients by the modification of a single substance (pre-processing), coprocessing of 2 or more components could be applied to produce composite particles or coprocessed excipients[4]. Coprocessed excipients by virtue of combining properties of two different excipients fulfill the increasing demand of multifunctional excipients for direct compression tabletting[5].

Coprocessed excipients are prepared by incorporating one excipient into the particle structure of another excipient using processes such as co-drying[6]. The coprocessed multi-component-based excipients are introduced to

***Corresponding author:**
Email: akolowosulu@yahoo.com

achieve better characteristics and tabletting properties than a single substance or the physical mixtures[4]. They have been developed primarily to address the issues of flowability, compressibility, and disintegration potential[6]. Several of these excipients are commercially available e.g. Ludipress (lactose, polyvinylpyrollidone and crosspovidone), Cellactose and Microlac (lactose and cellulose), StarLac (starch and lactose), Prosolv (microcrystalline cellulose and silicon dioxide)[3,4,6,7] etc.

This research work is geared towards development of new coprocessed excipients consisting of starch and acacia gum for use in direct compression tabletting. Starches from many sources have long been used in tablet formulations as diluents, binder, and disintegrant[8]. On the other hand, acacia is mainly used in oral and topical pharmaceutical formulations as suspending and emulsifying agent. It is also used in the preparation of pastilles and lozenges, and as tablet binder[8]. Acacia gum when used as tablet binder forms a very strong compact[8]. Therefore, coprocessing maize starch and acacia to form a new product should combine good flowability and stronger compact due to acacia and rapid disintegration of native maize starch. Improved fluidity and compactibility of the new coprocessed excipient consisting maize starch and acacia should make it suitable for direct tableting process.

A review of the literature yielded no report on the combination of maize starch and acacia gum used to form a coprocessed excipient. This is the first time that maize starch and acacia gum are combined together to form a coprocessed excipient for use in direct compression tabletting. This paper describes the preparation of novel coprocessed excipients of maize starch and acacia using simple technique of co-drying their well dispersed aqueous slurry. The results of physical and tablet properties of *StarAc* thus produced are also reported in this paper.

MATERIALS AND METHODS

MATERIALS

The materials used are of pharmaceutical grade, namely; maize starch (BDH Chemical, England) and acacia gum (Hopkins &Williams, England).

METHODS

Preparation of Coprocessed Excipients

Suspensions were prepared from mixtures of maize starch MS and acacia gum AC to have different ratios of MS powder and AC of 97.5:2.5, 95.0:5.0, 92.5:7.5 and 90.0:10.0. The required proportions of MS were dispersed in distilled water necessary to have the final solid content of suspensions of 40% w/w. A two-litre suspension was prepared for each combination. The required amount of acacia gum was also dispersed in distilled water. Then, the dispersion of the gum was mixed with the MS slurry thoroughly with the aid of a stirrer for 10 minutes to obtain a homogenous suspension of the required ratio. The mixed suspension was heated on a water-bath thermostatically maintained at a temperature of 80°C for 15 minutes[8,9] with constant stirring until gelatinisation (fully pregelatinized maize starch and acacia [FPMSAC]). The mixture was subsequently poured on a tray and dried in hot air oven (Gallenkamp, UK) at temperature of 60 ºC for 48 h. The dried mass was powdered in a laboratory mill. Similarly, to obtain partial pregelatinized mixtures; the aqueous slurry of the required MS was dispersed in distilled water and mixed with aqueous dispersions of the required amount of AC under continuous stirring for 10 minutes. The mixed suspensions was heated on a water-bath thermostatically maintained at a temperature of 55°C (i.e. below the gelatinization temperature) for 15 minutes (partially pregelatinized maize starch and acacia [PPMSAC]), the resultant paste was dried in hot air oven at temperature of 60 ºC for 48 h[8,10]. Similarly, MS alone without acacia gum (pregelatinized starch) was also produced using the same conditions as described above for both full pregelanization (fully pregelatinized maize starch [FPMS]) and partial pregelanization (partially pregelatinized maize starch [PPMS]).

Studies on Physical Properties of Coprocessed Excipients

Bulk Density and Tapped density determination

A 10 g quantity each of the powder samples was, placed into a clean 50 ml measuring cylinder and the volume, V_0 (bulk volume), occupied by each of the samples without tapping was noted. The cylinder was tapped 500 times on a hard table top and tapped volume, V_{500} were recorded. The experiment was repeated in triplicates. The bulk and tapped densities were calculated as the ratio of mass to volume (V_0 and V_{500} respectively)[11].

Carr's Compressibility Index and Hausner's ratio:

This is the percentage difference between the tapped density and the bulk density. Also referred to as compressibility index[12].

Hausner's ratio is the ratio of the tapped density to bulk density[13].

Flow Rate

A 10 g of sample of powder was passed through the Erweka flowability tester (Type: GDT, Germany). The time taken for the sample to flow was recorded. This

experiment was repeated three times and the average reading recorded in g/sec.

Angle of Repose

A clean glass funnel was clamped on a retort stand such that the perpendicular height of the tip of the funnel was 10 cm from the flat table surface with a clean sheet of paper. 10 g of StarAc was poured into the funnel, with opening of funnel blocked with a cotton wool. This was removed and a powdered heap was formed. The height was measured as H (cm). The diameter of the circumference of the heap was divided to give the radius, R.

$$Tan\ \alpha = H/R \qquad \text{Equation 1}$$

Where α =angle of repose, H= height of the of powder and R=radius of heap base

Preparation of placebo StarAc tablets

300 mg of the different samples of the coprocessed excipient (StarAc) were directly compressed into tablets using the single stroke tablet press machine (Korsch, EKO, Germany) at compression force of 5.5 – 7.5 metric tonne. The placebo tablets thus produced were subjected to various in-process quality control tests as described below.

Evaluation of Tablets:

Determination of Tablet Weight, Diameter and thickness

20 tablets weighed as a whole and then individually. The digital caliper was used to measure the diameters and thickness of 10 tablets randomly picked tablets. The mean and standard deviation was calculated.

Friability Test and Crushing strength

The friability of 10 tablets was determined using Roche Friabilator (TA3R Erweka, Germany) at a rotation speed of 25 rpm for 4 minutes. The tablets were removed, dusted and weighed. Percentage of weight loss was determined. The crushing strength of tablets from each batch was determined using Monsanto hardness tester (Manesty, England). The results are the average of 10 determinations

Tablet Disintegration Test:

The disintegration time of tablet was determined on 6 tablets in deionized water at 37°C ± 1°C using USP disintegration test apparatus (ZT3, Erweka, Germany). The time taken for each tablet to disintegrate and pass through the mesh was noted. The data given are average of 6 determinations.

RESULTS AND DISCUSSION

The results of micromeritic properties of various batches of coprocessed excipients at different mixing ratios using the fully pregelatinized methods are shown in Table 1.

The results show that the bulk densities of the coprocessed excipients made using the fully pregelatinized method (FPMSAC) increase as acacia gum increases in the coprocessed excipient. However, the tapped densities were relatively constant from batch III (containing 5% of gum) to Batch V (containing 10% of gum). Furthermore, the angle of repose, Carr's index (CI) and Hausner ratio (HR) decreased with the content of acacia gum in the coprocessed excipients, while the flow rate increased with increasing gum concentrations. The coprocessed excipients (FPMSAC) exhibited a better flow property than the pregelatinized starch (batch without acacia gum) i.e. batch I (FPMS).

Similarly, the results of micromeritic properties of various batches of coprocessed excipient at different mixing ratios using the partial pregelatinization methods (PPMSAC) are shown in Table 1.

The results of the bulk densities, tapped densities and angle of repose did not show any trend with increase in acacia content of coprocessed excipients. However, the CI and HR values decrease with increase in acacia gum concentration in the coprocessed excipients. The flow rate of the excipient also increased with the concentration of acacia in the coprocessed excipients. The coprocessed excipients (PPMSAC) exhibited a better flow property than the pregelatinized starch (batch hout m) i.e. batch VI (PPMS).

The results obtained from the powder flowability studies show that the flow of the coprocessed excipients improved with increasing concentration of acacia gum in the coprocessed excipients. The flowability of maize starch is very poor because of the small size of starch grains[4]. Therefore, in order to improve the flow of the maize starch, the starch particles have to be enlarged. This can be achieved by agglomeration of the starch particles in order to make them larger. Pregelatinization is one of the main ways of achieving particle size enlargement of starch particles[4,14] . Zhang *et al*[15]considered the physical properties of commonly used direct compression excipients and concluded that pregelatinized starch generally exhibited moderate flowability, compressibility and hardness.

Table 1 Micromeritic properties of fully and partially pre-gelatinized StarAc

Batch[a]	Micromeritic Properties					
	Bulk density ($g\ cm^{-3}$)	Tapped density ($g\ cm^{-3}$)	Angle of Repose (°)	Flow rate ($g\ sec^{-1}$)	Carr's index (%)	Hausner's ratio
I	0.63 (0.02)[b]	0.80 (0.07)	30.9° (1.23)	9.31 (0.49)	21.00 (1.47)	1.26 (0.08)
II	0.63 (0.01)	0.75 (0.04)	30.2° (0.84)	10.2 (0.52)	14.9 (5.62)	1.19 (0.05)
III	0.67 (0.01)	0.77 (0.01)	26.8° (2.11)	12.4 (0.50)	13.04 (1.23)	1.15 (0.02)
IV	0.71 (0.02)	0.77 (0.00)	25.5° (2.39)	12.9 (0.23)	7.36 (1.50)	1.08 (0.02)
V	0.72 (0.00)	0.77 (0.00)	24.5° (0.95)	15.4 (0.29)	6.49 (0.00)	1.07 (0.00)
VI	0.56 (0.02)	0.71 (0.07)	28.1° (1.23)	6.30 (0.17)	21.00 (1.47)	1.27 (0.08)
VII	0.58 (0.01)	0.67 (0.01)	27.2° (0.63)	7.97 (1.30)	13.5 (1.49)	1.16 (0.02)
VIII	0.52 (0.01)	0.59 (0.01)	28.8° (1.27)	10.0 (0.00)	11.78 (2.79)	1.13 (0.04)
IX	0.56 (0.00)	0.63 (0.00)	30.3° (0.75)	11.0 (0.14)	11.11 (0.00)	1.13 (0.02)
X	0.58 (0.01)	0.64 (0.01)	29.6° (0.47)	9.44 (0.18)	10.35 (1.70)	1.12 (0.02)

[a]Key: I (FPMS), II (FPMSAC97.5:2.5), III (FPMSAC95:5), IV (FPMSAC92.5:7.5) , V (FPMSAC90:10), VI (PPMS), VII (PPMSAC97.5:2.5), VIII (PPMSAC95:5), IX (PPMSAC92.5:7.5) and X (PPMSAC90:10).
[b]Values in parentheses are standard deviations *n* = 3.

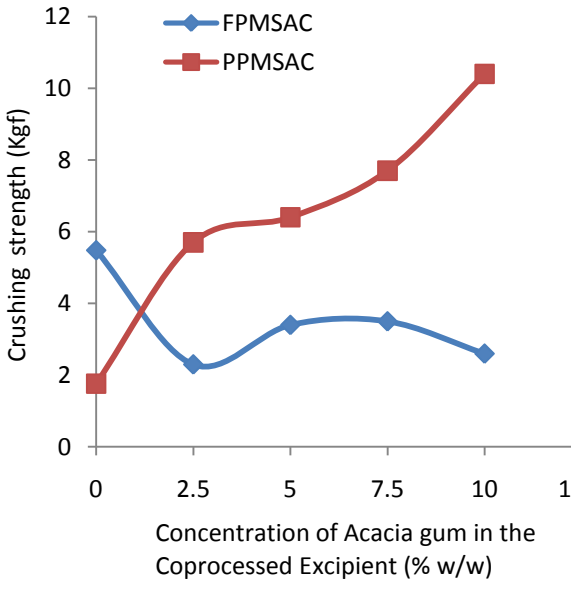

Fig. 1 Effect of concentration of acacia gum in coprocessed excipients on the crushing strength

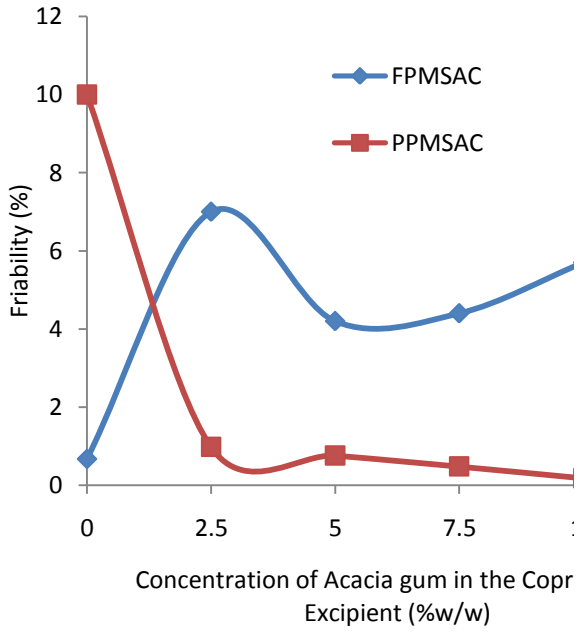

Fig. 2 Effect of concentration of acacia gum in coprocessed excipients on tablet friability

Table 2 Tablet properties of fully and partially pregelatinised StarAc

Batch[a]	Tablet Properties					
	Mean weight (g)	Diameter (mm)	Thickness (mm)	Crushing strength (Kgf)	Friability (%)	Disintegration time (min)
I	0.30 (0.01)[b]	10.03 (0.01)	3.53 (0.06)	5.48 (0.23)	0.67 (0.72)	2.2 (0.75)
II	0.30 (0.01)	10.07 (0.02)	3.58 (0.03)	2.3 (0.33)	7.0 (0.68)	3.47 (0.58)
III	0.31 (0.01)	10.07 (0.02)	3.60 (0.03)	3.4 (0.48)	4.2 (2.34)	3.84 (0.36)
IV	0.30 (0.01)	10.01 (0.01)	3.36 (0.03)	3.5 (0.46)	4.4 (1.00)	4.77 (0.80)
V	0.30 (0.01)	10.01 (0.01)	3.45 (0.03)	2.6 (0.70)	5.7 (0.59)	9.38 (1.00)
VI	0.30 (0.04)	10.11 (0.04)	3.57 (0.11)	1.76 (0.33)	10.0 (0.54)	0.43 (0.62)
VII	0.30 (0.01)	10.00 (0.03)	3.40 (0.07)	5.7 (0.13)	0.98 (0.65)	2.22 (0.46)
VIII	0.30 (0.01)	10.01 (0.02)	3.36 (0.05)	6.4 (0.34)	0.76 (0.12)	4.08 (0.49)
IX	0.30 (0.01)	10.02 (0.02)	3.43 (0.05)	7.7 (0.85)	0.48 (0.46)	8.89 (0.58)
X	0.30 (0.01)	10.01 (0.02)	3.24 (0.05)	10.4 (0.40	0.18 (0.09)	12.28 (0.60)

[a]Key: I (FPMS), II (FPMSAC97.5:2.5), III (FPMSAC95:5), IV (FPMSAC92.5:7.5) , V (FPMSAC90:10), VI (PPMS), VII (PPMSAC97.5:2.5), VIII (PPMSAC95:5), IX (PPMSAC92.5:7.5) and X (PPMSAC90:10).
[b]Values in parentheses are standard deviations *n* = 3.

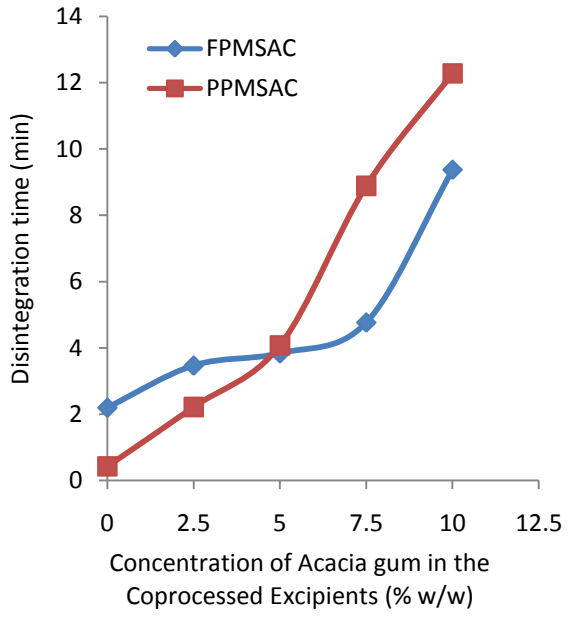

Fig. 3 Effect of concentration of acacia gum in coprocessed excipients on the disintegration time

The coprocessed excipients consisting of maize starch and acacia gum (StarAc) studied in this work exhibited a better flow property compared with the pregelatinized starches (FPMS & PPMS) produced using the fully- and partially pregelatinization methods (the pregelatinized starches were prepared locally in the laboratory). The unsatisfactory flow of FPMS & PPMS compared with the coprocessed excipients may be due to presence of greater amount of fines in its particle structure. The coprocessed excipients have smaller amounts of fines because of particle size enlargement due to the presence of acacia in their particle structure. The acacia gum serves as adhesive and it brings together small starch particles into larger, permanent aggregate (composite particles). Furthermore, during preparation of the coprocessed excipients heat was used which could induce partial and full gelatinization of the starch grains, resulting in the formation of solid bridges when the mixed suspension was dried; these solid bridges assisted the starch particles in adhering together to form granular or aggregated particles[4], which was further enhanced by the presence of acacia gum in particle structure of maize starch.

The flowability of StarAc depended on the method used to produce them and on the concentration of acacia gum present in the coprocessed excipients. The StarAc produced using the fully pregelatinized method (FPMSAC) exhibited a better flow property as evidenced from all the indices used for evaluation than those produced using the partial pregelatinized method (PPMSAC). This is probably due to the fact that the FPMSAC have larger particles and favourable particle size distribution than PPMSAC.

The results of tabletting properties of placebo tablets made with fully pregelatinized StarAc are presented in Table 2. The mean weight and the tablet dimensions (diameter and thickness) did not show any significant variations. However, an unexpected decrease in crushing strength values in the range (2.3 – 3.5 Kgf) was observed in the coprocessed excipients produced using full pregelatinization method compared with pregelatinized starch (FPMS) i.e. batch I which had a crushing strength of 5.48 Kgf. The various batches of coprocessed excipients FPMSAC (Batch II – V) were expected to have higher crushing strength values than FPMS (pregelatinized starch) because they contain a strength enhancing agent, namely; acacia in their particle structure.

The loss of compactibility observed in coprocessed excipients also reflected in result of the tablet friability. Expectedly, all the coprocessed excipients failed the friability test. The friability values for batch II – V were in the range of 4.2 – 7.0 Kgf. Therefore, tablets produced with coprocessed excipients using the fully pregelatinization method were unsatisfactory in terms of strength and friability of compact. However, all the tablets produced with FPMSAC disintegrated within 15 minutes. And the disintegration time was directly proportional to the amount of acacia gum present in the coprocessed excipients. However, the unexpected decrease in crushing strength and increase in friability that was observed for the FPMSAC may be due to electrostatic forces preventing adhesion of particles to one another. The particles of the FPMSAC may have acquired surface charges as a result of longer milling time required to obtain particles of desired sizes of the coprocessed excipients. The coprocessed excipients produced using the fully pregelatinization method on drying formed very hard compact which required longer milling time of 30 minutes.

The result of tabletting properties of placebo tablets made with partially pregelatinization method PPMSAC is also presented in Table 2. The mean weight and the tablet dimensions (diameter and thickness) did not show any significant variations. The range of values of the crushing strength and the friability for tablet made from PPMSAC is 5.7 – 10.4 Kgf and 0.98 – 0.18% respectively. The crushing strength values increased and the friability values decreased proportionally as the content of acacia in the coprocessed excipient increased. Similarly, all the PPMSAC excipients disintegrated within 15 minutes. Uncoated tablet according to BP[16] is expected to disintegrate within 15 minutes.

The effect of the acacia gum content of the coprocessed excipient made by full- and partial pregelatinization on the crushing strength, friability and disintegration time are depicted in Fig 1-3. It can be seen from the figures that the crushing strength of the placebo tablet made with PPMSAC was directly proportional to the content of acacia in the coprocessed excipients, whereas a decrease in crushing strength was observed for FPMSAC. 0% acacia gum concentration represent the batch which had no gum i.e. the pregelatinized starches FPMS and PPMS respectively. PPMSAC had higher crushing strength and lower friability values than FPMSAC at all concentrations of acacia gum employed.

The results of the tablet properties evaluation showed that PPMSAC show a general increase in the crushing strength value as the concentration of the acacia gum in the coprocessed excipient increases. This could be due to the fact that there exist more particle – particle contact points; particularly with particles of the gum, which help to create more solid bonds hence, higher crushing strength values were obtained. It is well established that the friability values tend to decrease and disintegration time tend to increase with the crushing strength for the same aforementioned reason for an increase in crushing strength.

On the basis of results of the crushing strength, friability and disintegration time the partial pregelatinization method was selected as the preferred method of producing the coprocessed excipients. Therefore, partially pregelatinized coprocessed excipient of MS and Ac could be developed for use in direct compression tabletting.

ACKNOWLEDGEMENT

This research was supported by grants from the Ahmadu Bello University Board of Research and Carnegie Corporation Projects in Ahmadu Bello University, Zaria, Nigeria.

REFERENCES

1. Rudnic, E.M and J.D. Schwartz, 2000. Oral Dosage Forms. In Remigton: The Science and Practice of Pharmacy, Ed, Gennaro, A.R. 20th Edition, Published by Philadelphia College of Pharmacy and Science. Pp.858-893.

2. Jivraj, M., L.G. Martini and C.M. Thomson, 2000. An overview of the different excipients useful for the direct compression of tablets. *PSTT*; 3(2):58-63

3. Hauschild, K. and K.M. Picker, 2004. Evaluation of a new coprocessed compound based on lactose and maize starch for tablet formulation. http//www.aapspharmsci.org, *AAPS PharmScitech,* 6: 27-38.

4. Limwong, V., N. Sutanthavibul, and P. Kulvanich, 2004. Spherical composite particles of rice starch and microcrystalline cellulose: A new coprocessed excipient for direct compression. *AAPS PharmSciTech*, 5(2): E30

5. Saha, S. and A.F. Shahiwala, 2009. Multifunctional coprocessed excipients for improved tabletting performance. *Expert Opinion on Drug Delivery* 6(2): 197-208.

6. Nachaegari SK and A.K. Bansal, 2004. Coprocessed excipients for solid dosage forms. *Pharmaceutical Technology,* 28:52-64

7. Gohel, M.C and P.D. Jogani, 2005. A review of co-processed directly compressible excipients. *Journal of Pharmacy and Pharmaceutical Science,* 8(1): 76-93.

8. Rowe, R.C., P.J. Sheskey, and S.C. Owen, Eds., 2006. Handbook of Pharmaceutical Excipients. Fifth Edition. Pharmaceutical Press and the American Pharmacists Association. Pp. 725-730.

9. Odeku, O.A., W. Schmidt, and K.M. Picker-Freyer, 2008. Material and tablet properties of pregelatinized (thermally modified) *Dioscorea* starches. *European Journal of Pharmaceutics and Biopharmaceutics.* 70:357-371

10. Alebiowu, G. and O.A. Itiola, 2007. Influence of process variables on release properties of paracetamol tablets. *Acta Pharm.,* 57:73-85.

11. Ohwoavworhua, F.O. and T.A. Adelakun, 2005. Some physical characteristics of microcrystalline cellulose obtained from raw cotton of *Cochlospermum planchonii*. Tropical *Journal of Pharmaceutical Research*, 4(2):501-507.

12. Carr, R.L., 1965. Classifying flow of solids. *Chemical Engineering,* 72:69-72

13. Hausner, H., 1967. Friction conditions in a mass of metal powder. *International Journal of Powder Metalurgy*; 3:7-13.

14. Alebiowu, G. and O.A. Itiola, 2002. Compressional characteristics of native and pregelatinized forms of sorghum, plantain, and corn starches and the mechanical properties of their tablets. *Drug Development and Industrial Pharmacy*; 28(6):663-672

15. Zhang, Y., Y. Law, and S. Chakrabarti, 2003. Physical properties and compact analysis of commonly used direct compression binders. *AAPS PharmSciTech*; 4(4): Article 62 (1-11).

16. British Pharmacopoeia, 2002. Tablet Disintegration tests for tablets and capsules Printed in the United Kingdom by The Stationery Office Limited.