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Research Paper

Evaluation of Flow Properties and Consolidation Characteristics of Co-processed Gelatin and Corn Starch

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ABSTRACT:*The aim of this work was to study the flow properties and consolidation characteristics of co-processed gelatin and corn starch as a direct compression excipient.Gelatin was co-processed with the corn starch at varying ratios (0.25:49.75, 0.5:49.5, 1:49, and 1.25:48.75) using pre-gelatinization method. The flow properties of the excipients were studied using standard methods such as bulk density, tapped density, particle density, Hausner ratio, Carr's index, angle of repose, particle shape and size. Co-processed excipient containing gelatin and corn starch batch B (0.5: 49.5) was found to give the best flow properties with bulk, tapped, and particle density of 0.55, 0.67, and 2.54 g/cm^3 respectively. It also gave angle of repose of 32.97^0 and Hausner ratio of 1.21. Only batch B gave Hausner ratio of less than 1.25 indicating good flow property and as a result, it would therefore be of advantage in direct compression tableting. From the results obtained, it can be concluded that co-processing gelatin with corn starch improved the flow properties and consolidation characteristics of its natives. This co-processed excipient can serve as a locally sourced alternative to costly commercially available directly compressible excipients such as Cellactose®80.*

KEYWORDS:*Gelatin, corn starch, co-processed excipient, flow properties, consolidation characteristics*

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I. INTRODUCTION

Tablets are the most commonly used solid pharmaceutical dosage form. Tablets comprise of a mixture of active pharmaceutical ingredients and excipients, usually in powder form, compressed from a powder into a solid dosage form. Pharmaceutical powders are generally irregular in shape. They also exhibit different densities, particle sizes and particle size distribution which limit their flow and compressibility. In the formulation of tablets, which usually involves a number of excipients in powdered form of different sizes, shape and densities; granulation process is embarked upon to unify the powders into granules that can easily flow and be compressible. The granules can be produced either by wet or dry granulation. Wet granulation method is suitable for drugs that are not sensitive to moisture and heat. Dry granulation method is suitable for drugs that are sensitive to moisture but not sensitive to heat. Direct compression method is suitable for moisture and heat sensitive drugs which involves the use of direct compression excipients. Direct compression excipients are specially processed to obtain almost spherical shaped powders. Existing direct compression excipients are very costly; as a result, there is need for the search for such excipient from local sources [1] and [2].

Direct compression excipients can be prepared by various methods which include co-processing. Co-processing is one of the most widely explored and commercially utilized methods for the preparation of directly compressible excipients[3] and [4]. Co-processed excipients are introduced to achieve better flow, better dilution potential, and reduced fill weight variation in comparison with a single substance or the physical admixture. Several of these excipients are commercially available. Examples include Cellactose® (lactose-cellulose), Avicel® CE-15 (microcrystalline cellulose and guar gum), Ludipress® (lactose, polyvinylpyrrolidone, and crosspovidone), and Prosolv® (microcrystalline cellulose and silicon dioxide) [5] and [6].

The overall production cost decreases because of improved functionality compared with individual excipients. They can retain functional advantages while selectively reducing disadvantages. This can be helpful in reducing the time required to develop formulations.

Gelatin can be obtained from the skin and bones of animals [7]. Gelatin co-processed with corn starch is expected to possess performance advantages that cannot be achieved using a physical admixture of the same combination of these two excipients. This study is aimed at evaluation of properties of co-processed gelatin and

corn starch in comparison with its natives, physical admixture of the two single excipients, and commercially available co-processed excipient Cellactose ® 80.

II. MATERIALS AND METHODS

Corn starch powder (Sigma-Aldrich, Malaysia), Gelatin powder from porcine skin (Sigma, USA), Cellactose ® 80 (gift from Katchey Company Ltd, Lagos, Nigeria).

2.1 Preparation of Co-processed Excipients

The method reported byOgunjimi and Alebiowu was adapted [8]. A 50 g gelatin and corn starch mixtures at various ratios listed in Table 1were co-processed respectively. Gelatin was dissolved in 50 mL of distilled water. 50 mL of water was added to the previously sieved corn starch to form slurry. The corn starch slurry was mixed thoroughly with gelatin solution. The homogenous mixture was kept in a water bath and stirred continuously until the temperature of 50℃ was attained. It was then dehydrated with acetone after which the supernatant was removed by passing the product through a muslin bag. The wet coherent mass was passed through a 355 µm mesh sieve. The wet co-processed granules were air-dried for 24 h, dry screened and then stored in a tightly closed glass bottle for further use. The batch ratio with good flow properties was used for the work.

Table 1: Formulae for preparation of batches of co-processed excipients

Materials	Batch Ratios			
	A	B	C	D
Gelatin	0.25	0.5	1	1.25
Corn Starch	49.75	49.5	49	48.75

2.2 Determination of Particle Size and Shape

The particle size and shape of gelatin, corn starch, co-processed excipient 0.5:49.5 (selected based on its flow properties), and Cellactose® 80 were determined using optical microscope (LEICA Galen III Research Microscope, USA) equipped with an integrated camera (Celestron digital microscope imager, model 44421, USA) on 300 particles randomly selected from the optical field. The photomicrographs taken were analyzed using Image-J software (Model 1.48v, Wayne Rasband, USA). The size and shape descriptors used in this study are defined below:

Aspect ratio = $\frac{b}{l}$ (1)

Elongation ratio = $\frac{l}{b}$ (2)

Roundness = $\frac{4\pi A}{p2}$ (3)

Irregularity= $\frac{p}{l}$ (4)

Equivalent circle diameter = $\sqrt[2]{A/\pi}$ (5)

Where:

b= length of minor axis (minimum Feret diameter)

l= Length of major diameter (maximum Feret diameter)

A= Projected area of the particle

P= Perimeter of the particle

2.3Determination of Flow Properties of Excipients

Particle density of gelatin, corn starch, co-processed excipients and Cellactose® 80 were determined using solvent pycnometric method. Acetone was used as the displacement fluid. The bulk density was determined by introducing 30 g of the excipients into a 100 mL measuring cylinder of known internal diameter. The bulk volume V_o was obtained by calculation from the height occupied by the excipient at zero pressure. The bulk density was calculated as weight per unit volume of the excipient. This was calculated as a mean of three determinations. The powder in the measuring cylinder was tapped 100 times on a soft padded table surface and the height was recorded. The tapped volume V_{100} was obtained by calculation from the height occupied by each of the excipient at 100 taps. This was calculated as a mean of three determinations. Hausner ratio was calculated as the ratio of tapped density to bulk density of the excipients. Carr's index was calculated from the relationship [(tapped density – bulk density)/tapped density] × 100. The angle of repose was determined by fixed height method. The porosity of excipients was determined from the equation 1-RD, where RD is the relative density obtained from the equation, RD = Bulk (loose) density/Particle density.

2.4Determination of Consolidation Characteristics of Excipients

These were determined by pouring 30 g of each excipient namely gelatin, corn starch, co-processed excipients of batches A to D, the physical admixture of the batch with the best flow property (0.5:49.5), and cellactose® 80 into a 100 mL measuring cylinder of known internal diameter. The measuring cylinder was held with hand like a fulcrum at a distance of 4.5 cm away from the surface, on a soft padded surface. The height at 20, 40, 60, 80 and 100 taps was noted and recorded. The data obtained was used to assess the consolidation behavior of the excipients using the method described by Ogunjimi and Alebiowu to study the relative decrease in powder volume and density change as a function of applied load [8].

$$\text{Log } \{(p_{td} - p_{bd}) / p_{td}\} = K \log N + C \quad (6)$$

where K and C are constants denoting the rate of consolidation and consolidation index, respectively, N is the number of taps, while P_{bd} and P_{td} are bulk density and the tapped density of the powder bed after Nth tap, respectively.

2.5 Statistical Analysis

Analysis of variance (ANOVA) was used to analyze the results obtained using Statistical Package for the Social Sciences (SPSS) software. This was used to determine if there were any statistical significant differences between the means of three groups.

III. RESULTS AND DISCUSSION

3.1 Morphological Properties of Excipients

The morphological properties of the excipients are shown in Table 2.

The aspect ratio and elongation ratios of the excipients were found to be in the range of0.24 to 0.70 and 1.41 to 4.12 respectively.

Table 2: Morphological properties of excipients

Excipients Properties	Gelatin	Corn starch	Co-processed excipient 0.5:49.5	Cellactose® 80
Aspect ratio	0.70	0.43	0.24	0.70
Elongation ratio	1.41	2.30	4.12	1.41
Roundness	1.57	0.65	0.73	1.57
Irregularity	2.0	2.15	1.99	2.0
Equivalent circle diameter (µm)	1.12	1.94	2.25	1.12

Aspect ratio varies between 0 and 1 with a perfect circle having aspect ratio of 1. Elongation ratio is the inverse of aspect ratio. Roundness is a measure of how the projected area of the particle resembles that of a perfect circle with a perfect circle having a roundness of 1. Irregularity measures the surface area compared to the size of the particle[8] and [9].The particles irregularity was found to be in the range of 1.99 to 2.15. The roundness of the particles of the excipients which was found to be in the range of 0.65 to 1.57 indicates that their roundness was close to a perfect circle with roundness of one. From the results, it was found that the particle size of corn starch was improved by co-processing it with gelatin, hence improving the flow property of the powders.

3.2 Flow Properties of Excipients

The bulk and tapped density of a powder describes its packing behavior during tableting[10] and [11]. An increase in the tapped density is an advantage in tableting because the fill volume of the die would be reduced. The bulk density of the co-processed excipients containing gelatin and corn starch is shown in Table 3. An increase in tapped density was observed in all the batches of the co-processed excipients. It was observed that batch A (0.25:49.75, gelatin: corn starch) gave minimum value of particle density 2.40 g/cm^3, while batch C (1:49, gelatin: corn starch) gave maximum value of particle density 2.59 g/cm^3. There is significant difference among the four batches ($p < 0.05$). This implies that the co-processed excipients possessed good flowability, and as a result, completefilling of the die, uniformity of weight and content of compressed tablets would be achieved when employed in tableting. The values of Hausner ratio and Carr's index of the batches of co-processed excipient are shown in Table 3. Hausner ratio has been used to predict the flow behaviour of powdered solids. As a general rule Hausner ratio values less than 1.25 indicates good flow, while greater than 1.25 indicates poor flow [11] and [12]. Only batch B gave Hausner ratio of less than 1.25 indicating good flow property and would therefore be of advantage in direct compressiontableting.

Table 3: Physical properties of co-processed excipients

Properties	Batch A 0.25: 49.75	Batch B 0.5: 49.5	Batch C 1: 49	Batch D 1.25: 48.75
Bulk density(g/cm^3)	0.55±0.20	0.55±0.20	0.56±0.00	0.57 ±0.01
Tapped density(g/cm^3)	0.71±0.20	0.67±0.05	0.73±0.05	0.72±0.2
Particle density(g/cm^3)	2.40±0.01	2.54±0.01	2.59±0.01	2.49±0.01
Angle of Repose (^{o})	36.73±1.10	32.97±0.06	34.10±1.0	37.41±2.0
Carr's index (%)	22.53	17.91	23.28	20.83
Hausner ratio	1.29	1.21	1.30	1.26

Table 4: Physical properties of excipients

Properties	Corn Starch	Gelatin	Physical admixture 0.5: 49.5	Co-processed excipient 0.5: 49.5	Cellactose®80
Bulk density (g/cm^3)	0.57±0.30	0.62±0.40	0.55±0.20	0.55±0.20	0.45±0.00
Tapped density(g/cm^3)	0.74±0.05	0.71±0.05	0.68±0.05	0.67±0.05	0.54±0.05
Particle density(g/cm^3)	2.54±0.01	2.27±0.01	2.54±0.01	2.54±0.01	2.59±0.01
Angle of Repose (^{o})	34.99±0.9	29.59±3.3	38.99±2.4	32.97±0.06	27.31±1.0
Carr's index (%)	23.38	12.30	18.95	17.91	15.77
Hausner ratio	1.305	1.14	1.23	1.21	1.18

The densities, angle of repose, Carr;s index, and Hausner ratio of gelatin, corn starch, co-processed excipient batch B (selected based on its flow properties), its physical admixture (0.5: 49.5) and Cellactose®80 are presented in Table 4. The angle of repose could be used as a qualitative measure of the cohesiveness or the tendency of powdered or granulated materials to flow, for instance, from hoppers through the feed frame into tableting machines. Such uniformity of flow will minimize weight variations in tablets produced [10].

An angle of repose less than 25^o is considered to have very good flow whereas 50^o is poor [11]. The angle of repose of the excipients are presented in Table 4. Comparing the angle of repose and Hausner ratio of the co-processed excipient with its physical admixture, the co-processed excipient possessed better flow thus will minimize tablet weight variation. There is significant difference among the excipients ($p < 0.05$). Although Cellactose®80 possessed better flowability in comparison to the co-processed excipient (0.5: 49.5).

3.3 Consolidation Characteristics of Excipients

The maximum volume reduction 'a' after tapping, obtained from the slope of the plot of a graph of N/C against Nis as shown in Table 5. A low value of 'a' indicates that the powder system has packed more densely on initial pouring into the cylinder, which implies that the powders were well packed before tapping. For powders with low 'a' tappings reduces the voids by displacing air from the powder bed without changing the particle size and shape [9]. Figures 1, 2 and Table 5 reflect the maximum volume reduction 'a' of the excipients. Co-processed excipient batch B compared well with its physical admixture but Cellactose®80 gave better result compared to co-processed excipient batch B. Figures 3 and 4 show the relationship between the log density change and log number of taps of the excipients. Table 5 shows the results obtained from the plotted graphs in Figures 3 and 4. This reflects the consolidation behavior of the excipients providing insight into the inter-particle movement during vibration or tapping. Co-processing the natives affected the consolidation rate which is the rate of packing of the powders/granules as well as consolidation index [9]. The rate of consolidation, K which is the measure of rate of packing of the powders and granules as well as consolidation index (CI) which is a measure of effect of packing on flow were found to be influenced by co-processing the excipients. The higher the consolidation index, the higher the flow of the excipient [8]. From the results shown in Table 5, it was found that co-processed excipient batch B gave the best result in comparison with other batches. It also compared well with its physical admixture but Cellactose®80 gave better consolidation rate and index in comparison with co-processed excipient batch B. The value of porosity for Cellactose®80 was found to be higher than the other excipients. The higher the porosity of a powder or granules the higher will be its flow ability. Table 6 shows the results obtained for the porosity of the excipients. From the results, it was found that co-processed excipient

batch B compared well with its physical admixture but Cellactose®80 gave better per cent porosity in comparison with co-processed excipient batch B.

Table 5: Consolidation characteristics of excipients

Excipient	Maximum volume reduction 'a' (%)	Rate of Consolidation (K)	Consolidation index (CI)
Gelatin	14	0.30	-1.48
Corn starch	78	0.83	-2.25
Physical admixture (0.5 : 49.5)	30	0.54	-1.81
Co-processed excipient 0.25:49.75 A	44	0.69	-2.03
Co-processed excipient 0.5:49.5 B	26	0.46	-1.67
Co-processed excipient 1:49 C	66	0.81	-2.25
Co-processed excipient 1.25:48.75 D	57	0.75	-2.20
Cellactose®80	18	0.33	-1.46

Table 6: Porosity of excipients

Excipient	Porosity
Gelatin	0.725
Corn starch	0.773
Co-processed excipient 0.25:49.75 A	0.771
Co-processed excipient 0.5:49.5 B	0.784
Co-processed excipient 1:49 C	0.785
Co-processed excipient 1.25:48.75 D	0.772
Physical admixture 0.5: 49.5	0.782
Cellactose®80	0.823

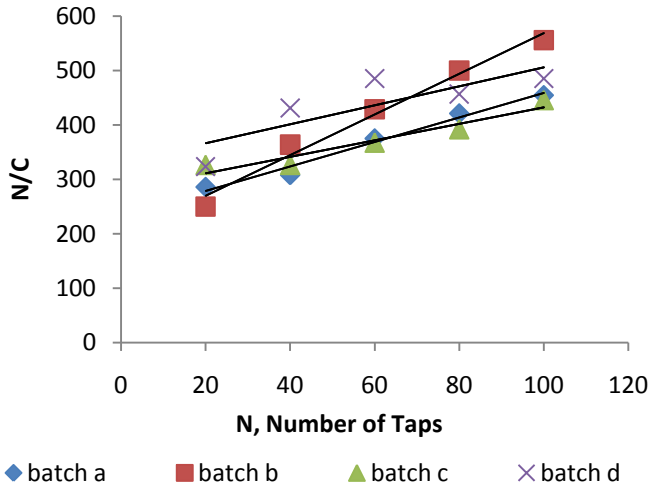

Figure 1: Plot of N/C against number of taps for the co-processed excipients (batches a –d)

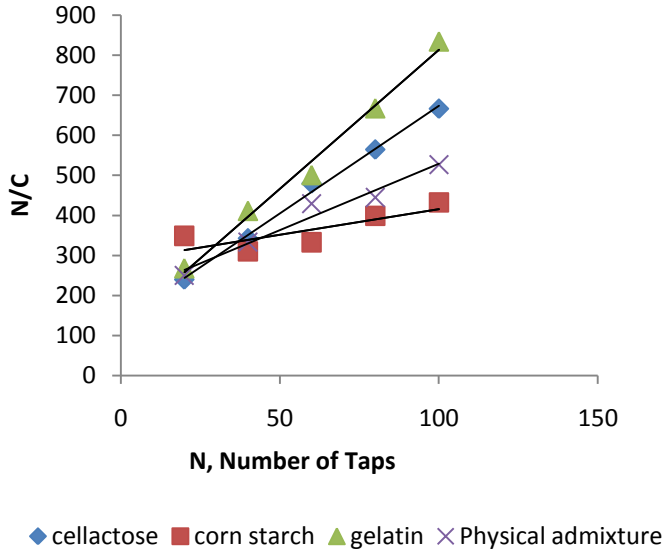

Figure 2: Plot of N/C against number of taps for cellactose®80, corn starch, gelatin, and physical admixture (0.5: 49.5)

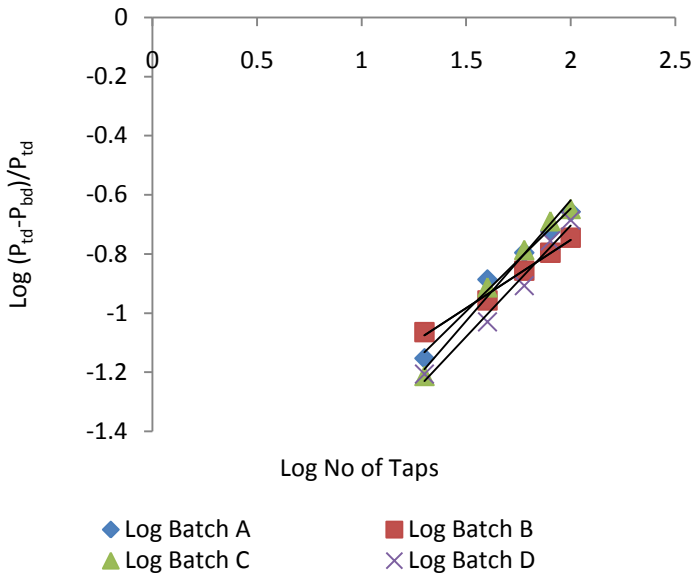

Figure 3: Plot of log $(P_{td} – P_{bd})/P_{td}$ against log no of taps for co-processed excipients of batches A – D

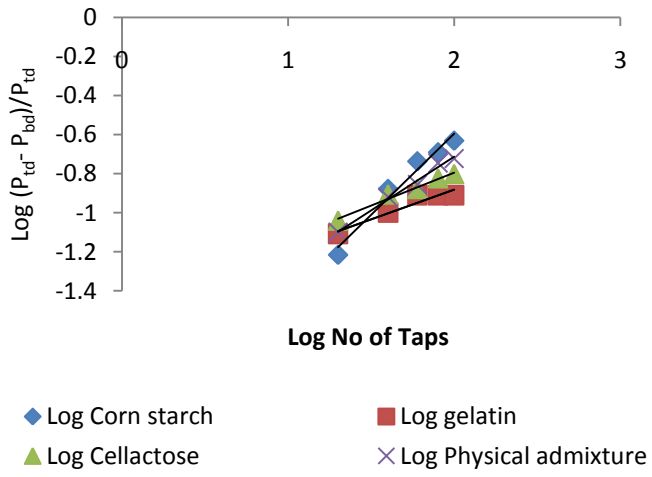

Figure 4: Plot of log $(p_{td} - p_{bd})/p_{td}$ against log number of taps for corn starch, gelatin, cellactose®80 and physical admixture (0.5: 49.5)

IV. CONCLUSION

Gelatin can be co-processed with corn starch to produce directly compressible excipient which can serve as a locally sourced alternative to costly commercially available directly compressible excipients such as Cellactose®80. Gelatin co-processed with corn starch possessed good flowability and consolidation properties and can be used in the formulation of directly compressible tablets. Hence, cost of production of tablets will be reduced and consequently the market price of such tablets will be lowered.

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