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Compaction and Tableting Behavior of a Novel Co-Processed Excipient in the Formulation of Metoprolol Succinate Tablets

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Pregelatinized starches exhibit good swelling and flow properties, imparting fast disintegration time but low mechanical strength in tablets. On the other hand, acacia gum acts as a binder in tablets by imparting high mechanical strength but prolonged disintegration time. Development of a co-processed excipient involving combination of the two excipients at sub-particle level will improve the functionality of the final product.

Objective: To develop a direct compressible co-processed excipient with pregelatinized cocoyam starch and acacia gum and to evaluate its compaction behavior and tableting properties in metoprolol succinate tablets.

Material and Methods: Batches of the co-processed excipient were prepared by co-fusion using different ratios (97.5:2.5; 95:5; 92.5:7.5; 90:10; 85:15; 80:20) of pregelatinized cocoyam starch and acacia gum. Flow and compaction properties and Fourier transform Infrared (FT-IR) analysis were carried out on native and pregelatinized starches and on the co-processed excipients. Metoprolol succinate tablets were formulated by direct compression using selected batches of co-processed excipients, pregelatinized cocoyam starch and acacia gum and then evaluated for mechanical strength and drug release.

Results: Pregelatinization produced starch with larger granules (138.75±59.21µm), improved swelling (2.03±0.00) and flow (flow rate 0.52±0.03g/s). The FTIR analysis of the co-processed excipients confirmed absence of chemical interaction. Flow properties, compressibility (Kawakita value, a = 0.190 – 0.223) and rate of packing (Consolidation rate, K = 0.1221 – 0.2551) of the co-processed excipients were enhanced. Metoprolol succinate tablets containing the co-processed excipients had higher mechanical strength (Crushing strength 106.03±15.80 MNm^{-2}) than those containing starch alone but faster drug release (disintegration time 1.80 ±0.20 -5.75±0.25; dissolution time; t_{80} 30-50 min) than those containing acacia gum. Cocoyam starch: acacia gum ratio 97.5:2.5 gave the optimum formulation with high crushing strength (106.03 ± 15.8MNm^{-2}) and fast release (t_{80} = 30 min).

Conclusion: Co-processed excipients of pregelatinized cocoyam starch and acacia gum could serve as suitable alternatives to other directly-compressible excipients for the formulation of tablets.

Keywords: Acacia gum, Cocoyam starch, Compaction properties, Co-processing, Metoprolol

INTRODUCTION

Co-processing is a particle engineering technique that combines two or more excipients at the sub-particle level with the aim of improving the functionality of the final product while minimizing the short-comings of the individual excipients (Nachaegari and Bansal, 2004; Patel and Patel, 2009). With co-processing, pharmaceutical manufacturers have the option of using a single excipient with multiple functional properties, thereby reducing the number of excipients in inventory.

Development of a co-processed excipient involves identifying two or more excipients to be co-processed by studying material characteristics and functionality requirements, selecting the proportions of excipients to optimize, assessing a suitable solvent in which to disperse the excipients, selecting an appropriate drying process and optimizing the process to avoid batch-to-batch product variations. Co-processed excipients have the advantage of a higher dilution potential (i.e. the ability of the excipient to retain its compressibility when diluted with another material) than a physical mixture of its constituent excipients (Flores *et al*, 2000), In addition, they have improved flow properties and improved compressibility profiles than the individual excipients (York, 1992). Also, studies have shown that after co-processing, the chemical properties of the individual excipients may not show any chemical change as no covalently bonded chemical entity is formed when the individual ingredients are combined to form the co-processed excipients (Saha 2009, Arane *et al*, 2014).

A large proportion of co-processed excipients that have been developed and commercialized for direct compression are either lactose-based or cellulose-based excipients (Armand *et al*, 2002; Gohel *et al*, 2003; Uma and Naheed 2014). In most tablet formulations, official or proprietary starches such as corn, rice and potato have been used. The high starch content of cocoyam (*Xanthosoma sagittifolium*, Araceae) makes it a source of starch that can be utilized in pharmaceutical tablet formulations. Modification of starch by pregelatinization will significantly improve swelling and enhance flow properties of the starch. However, the loss of viscosity and low thickening power when compared to the native starch is a limitation. Hence, pregelatinized starches have low crushing strength-friability ratios, imparting poor mechanical strength to tablets (Olowosulu *et al*, 2011). On the other hand, acacia gum, when used as a binder in tablet formulations, forms strong tablets with prolonged disintegration time (Ogunjimi and Alebiowu, 2014; Shayoub *et al*, 2015), a major limitation in tablet formulations of drugs that are required for immediate release. Combination of pregelatinized cocoyam starch with acacia gum as a co-processed excipient is expected to improve flowability and compactibility, producing a new suitable excipient for direct tableting process. Agglomeration of starch particles by addition of acacia gum will result in particle size enlargement, forming permanent aggregates which will improve flowability and compact hardness of the co-processed excipient (Olowosulu *et al*, 2011).

The aim of this study is to develop a directly-compressible co-processed excipient using pre-gelatinized cocoyam starch and acacia gum mixed at different ratios. Selected co-processed combinations of these excipients would then be used in the formulation of tablets of metoprolol succinate and evaluated for tablet mechanical strength and release properties. Metoprolol succinate, a 1-selective adrenergic blocking agent widely used in the treatment of hypertension, angina pectoris, and arrhythmias, is administered at an oral dose of 100 - 400 mg daily (Al-Saidan *et al*, 2004; BP, 1998**).** Immediate release of metoprolol succinate is essential in the management of cardiovascular disorders.

METHODOLOGY

Material and methods

Cocoyam tubers were purchased in a local market in Ibadan, Oyo State. Acacia gum was from Loba Chemie, Tarapur M.I.D.C., Vijay colony, India. Metoprolol succinate was obtained from Xi'an Sgonek Biological Technology Co.Ltd, Xi'an City, China. Xylene was obtained from R&D laboratories Ltd, Northern Ireland, UK. All other reagents were of analytical grade.

Starch extraction and modification

Starch was extracted from cocoyam tubers as reported in a previous method (Okunlola, 2018). Starch was extracted from cocoyam tubers that were peeled and diced into small pieces. The pieces of cocoyam tubers were soaked in distilled water containing sodium metabisulphite. The mixture was blended to obtain slurry that was strained through muslin cloth followed by sedimentation of the filtrate. The supernatant was decanted at 12 hours intervals and the starch slurry re-suspended in distilled water. The starch cake was collected after 72 hours and dried in a hot air oven at 60 °C for 48 hours. The dried mass was pulverized and then screened through a sieve of size 250 µm.

To pregelatinize cocoyam starch, aqueous slurry of native starch was obtained from 500 g of starch powder dispersed in 2 liters of distilled water. The slurry was heated at 70 ^{o}C with stirring for 45 minutes. The resulting paste was dried in hot air oven at 50 ^{o} C for 48 hours. The dried mass was powdered and sieved using a sieve of mesh size 250 µm and stored.

Preparation of the co-processed excipients of pregelatinized cocoyam starch and acacia gum

A batch of 100 g comprising of pre-gelatinized cocoyam starch and acacia gum at varying ratios of 97.5:2.5, 95:5, 92.5:7.5, 90:10, 85:15, 80:20 were prepared as described below:

For each batch, the required quantity of acacia gum was dissolved in sufficient quantity of distilled water to form a homogenous dispersion. Distilled water was added to the required amounts of cocoyam starch powder to form a slurry. Both dispersions of excipients were heated separately over a water bath. The gum dispersion was added to the starch slurry whilst stirring for 20 minutes at low heat (40 ^{o}C). The resulting homogenous mass was dried in a hot air oven (Gallenkamp BS oven 250 size 1, UK) at 40 ^{o}C for 72 hours. The dried mass was then milled, sieved with a mesh (250 µm) and stored in well-sealed containers.

Characterization of native and pregelatinized Cocoyam starches and co-processed excipients

Morphology

The morphology of the starches and co-processed excipients was observed using a scanning electron microscope (VEGA3 TESCAN, Germany) at an accelerating potential of 15.0 kV. All samples were super coated with gold prior to examination.

Fourier transform Infrared (FT-IR) analysis

The starches and co-processed excipients were analyzed by FTIR (FTIR-Thermo Nicolet Nexus 870 Madison, WI, USA) in transmission mode. Transmission spectra were recorded using at least 64 scans with 8cm^{-1} resolution in the spectral range 4000 - 400cm^{-1}.

Swelling index

The powder sample (5.0 g) was poured into a 100 mL measuring cylinder and the volume occupied was noted (V_1). Distilled water (90 mL) was added; the dispersion shaken for 2 minutes and then made up to volume. The slurry was allowed to stand for 24 hours before the sedimentation volume was read (V_2). The swelling index was calculated as V_2 / V_1. Determinations were done in triplicate.

Density measurements

A 50-mL pycnometer was weighed empty (W), filled with the non-solvent (xylene) and the excess wiped off. The weight of the pycnometer with the non-solvent was determined (W1). The difference in weight was calculated as W2. A 2.0 g quantity of the sample was weighed (W3) and quantitatively transferred into the pycnometer bottle. The excess non-solvent was wiped off the pycnometer and weighed again (W4). The particle density was calculated from the equation:

$$\frac{W2.W3}{50\ (W3 - W4 + W2 + W)\text{gcm} - 3} \quad (1)$$

The bulk density was determined by pouring 10 g of powder at an angle of 45° through a funnel into a glass measuring cylinder with a volume of 50 mL. The bulk density was measured as the ratio of mass to volume occupied by the sample. The tapped density was measured by applying 100 taps to 10 g of each powder sample in a graduated cylinder) at a standardized rate of 30 taps per minute. All determinations were done in triplicate.

Flowabillity

The flowability of each sample was evaluated using the Hausner's ratio and Carr's index:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad (2)$$

$$\text{Carr's Index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \text{ x } 100 \quad (3)$$

Angle of repose

Each powder sample (5 g) was allowed to flow freely through a funnel under gravity, to form a conical heap. The angle of repose was calculated from:

$$\text{Tan } \emptyset = {}^{h}/_{r} \quad (4)$$

where h is the height of the powder and r is the radius of the base of the cone. The angle of repose was calculated from the mean of three determinations.

Flow rate

The flow rate of the powder sample was obtained by determining the time "t" it took 30 g of the powder to pass through the orifice of a 10 mL pipette. The flow rate was calculated as mean of three determinations according to:

$$\text{Flow rate} = \frac{30\text{ g}}{\text{t}} \quad (5)$$

Viscosity
The viscosity of aqueous slurries of the native and pregelatinized starches (2%w/v) were determined using the Brookfield rheometer (DV-111+ model, Brookfield Engineering, USA) with spindle no. 3.

Angle of internal friction.
Porosity of the powder bed of all batches was determined using the equation below:

$$€ = 1 - \frac{Pb}{Pt} \quad (6)$$

where P_b = bulk density and P_t = true density

Plotting $€^2n / (1- €)$ (porosity factor) against n gives a straight line with intercept Ky on the y axis, where n is the number of taps. The angle made between the ordinate line and the abscissa is termed the angle of internal friction.

Compaction properties of co-processed excipients
Co-processed excipients, pregelatinized cocoyam starch and acacia gum (30 g each) was allowed to flow freely through a funnel into a glass measuring cylinder. The volume occupied by the starch powder was noted. Hundred taps were applied to the starch powder and the volume occupied after each set of 10 taps was determined. The volume reduction of the powders due to tapping was evaluated using the Kawakita analysis:

$$N/C = N/a + 1/ab \quad (7)$$

where N is the number of taps and both a and b are constants. Constant *a* describes the compressibility while the reciprocal of the constant *b* describes cohesiveness of powders or the time for onset of final packing. Term C describes volume reduction during the tapping and can be calculated from the equation:

$$C = \frac{(V0 - V)}{V0} \quad (8)$$

where V_o is the loose volume of the powder before tapping and V is the volume of the powder after a certain number of taps.

The data obtained from the densities were also used to access the consolidation behaviour of the excipients using the method described by Neumann *et al* (1967) to study the relative decrease in powder volume and density as function of applied load according to the equation below:

$$\text{Log } (\rho_T - \rho_B) / \rho_T = K \text{ Log } N + C \quad (9)$$

where ρ_T and ρ_B are the tapped and bulk densities respectively.

N is the number of taps.

C is the consolidation index.

K is the rate of consolidation.

Formulation of metoprolol succinate tablets
Two hundred grams of tablet formulations was prepared by mixing metoprolol succinate (50 $\%^w/_w$) with sodium starch glycolate (4%w/w), talc (2%w/w) and the selected co-processed excipients or individual excipient (43% $^w/_w$). Magnesium stearate (1%$^w/_w$) was added just before blending. Blends of metoprolol formulations (400 mg) were compressed for 30 s with a predetermined load (113 Mpa pressure) on a Carver hydraulic press (model C, Carver Inc. Menomonee Falls, WI) using a 10.5mm die.

Evaluation of metoprolol tablets

Fourier Transform Infra-red analysis
The FTIR of pure drug, metoprolol succinate tablets containing the co-processed excipient (in powder form), were analyzed by FTIR (FTIR-Thermo Nicolet Nexus 870 Madison, WI, USA) in transmission mode. Transmission spectra were recorded using at least 64 scans with 8 cm^{-1} resolution in the spectral range 4000–400 cm^{-1}.

Tablet weight and thickness
Twenty tablets were selected at random and their average weight was determined within ± 1mg using a weighing balance (Mettler PC 440 Delta range®, CH-8606 Greifensee-Zurich, Switzerland). Using a micrometer screw gauge, the thickness of twenty tablets was measured within ± 0.01mm.

Mechanical strength of tablets
The crushing strength of the tablets were determined at room temperature (27 ± 2°C) by diametral compression using a tablet hardness tester (DBK Instruments Mumbai, India). The results were taken only from tablets which split cleanly into two halves without any sign of lamination. The percent friability of the tablets was determined using a friabilator (DBK Instruments, England) operated at 25 rpm for 4 minutes.

Release properties of tablets

Disintegration time
The disintegration time of the tablets was determined in distilled water at 37±0.5 °C using a disintegration tester (DBK Instrument, England).

Assay of drug content
Ten tablets were crushed and dissolved in Phosphate buffer pH 6.8 and assayed for drug content using a UV/Visible Spectrophotometer (Jenway UV-7804c print, England) at wavelength 270 nm to determine the amount of metoprolol in the tablets.

***In vitro* dissolution test**
Dissolution test was carried out on the tablets using the USPXX III paddle method at 100 rpm in 900 mL of phosphate buffer (pH 6.8) maintained at a temperature of at 37±0.5 °C for 8 hours. Samples (10 ml) were withdrawn and replaced with equal amounts of fresh medium. The sample was diluted and the amount of metoprolol released was determined at wavelength of 270 nm using a UV/Visible Spectrophotometer (Jenway UV-7804c print, England).

RESULTS AND DISCUSSION

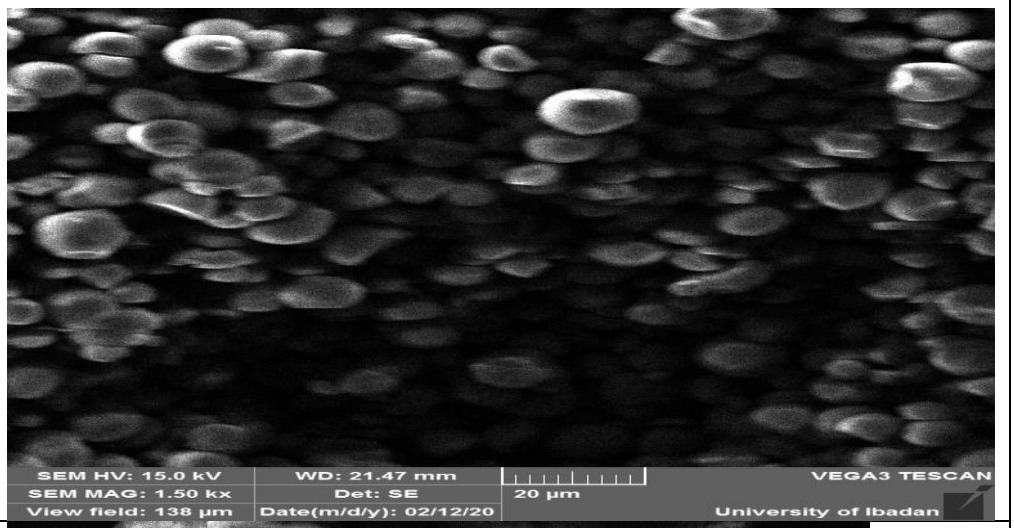
Material and physicochemical properties of native and pregelatinized cocoyam starches

The percentage yield of the cocoyam starch was 12.48 %w/w and this was considered satisfactory in conformity with literature report (Arawande and Ashogbon, 2019).

The Scanning electron microscope (SEM) images of native and pregelatinized Cocoyam starches are presented in Figure 1. The SEM of the native starch showed ovoid and polygonal-shaped granules with mean particle size of 6.24 ± 1.79 µm. The particle size was observed to increase on modification by pregelatinization, forming aggregates with irregular shape and mean size of 138.75 ± 59.21 µm. The presence of large void spaces, which is characteristic of the larger particles, gives a limited surface area available for inter-particulate bonding resulting in improved flow of the modified starch (Alebiowu and Itiola, 2002). The FTIR spectra of the starches are presented in Figure 2. The spectra revealed the formation of amorphous structure on pregelatinization of Cocoyam starch, resulting in decrease in the ordered structure of the native starch. This disruption is characterized by reduction in the band intensity at 1042cm^{-1} which was confirmed by the SEM images of the pregelatinized starches that showed irregular-shaped granules. In addition, the FTIR spectra of pregelatinized cocoyam starch showed four peaks at 3000 - 2500 cm^{-1} representing O-H and C-H stretching of carboxylic acid while the absorption peak at 1000 cm^{-1} indicated the presence of ether compounds with the molecular motion of carbon to carbon oxygen stretching vibration (Shuhada *et al*, 2013).

The result of the swelling index, particle, bulk and tapped densities are presented in Table 1. The swelling index of powder can be defined as the increase in the volume or weight of starch when allowed to swell freely in water. Pregelatinized Cocoyam starch showed significantly higher swelling than the native form. The swelling index of starches is of great importance in tablet formulation because the disintegrating properties of starches appear to be influenced by their swelling and wicking action (Musa *et a*l, 2008). Starches with higher swelling power would be expected to release the active pharmaceutical ingredient from their tablet compacts at a faster rate (Adebayo and Itiola, 1988).

(a)



(b)

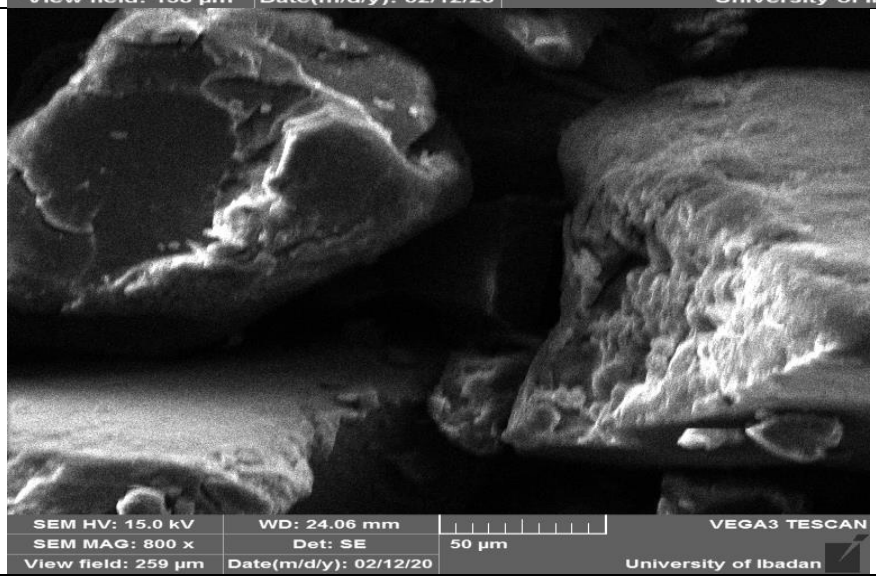


Figure 1: Scanning electron micrographs (SEM) of (a) native and (b) pregelatinized cocoyam starches (Mg x 800)

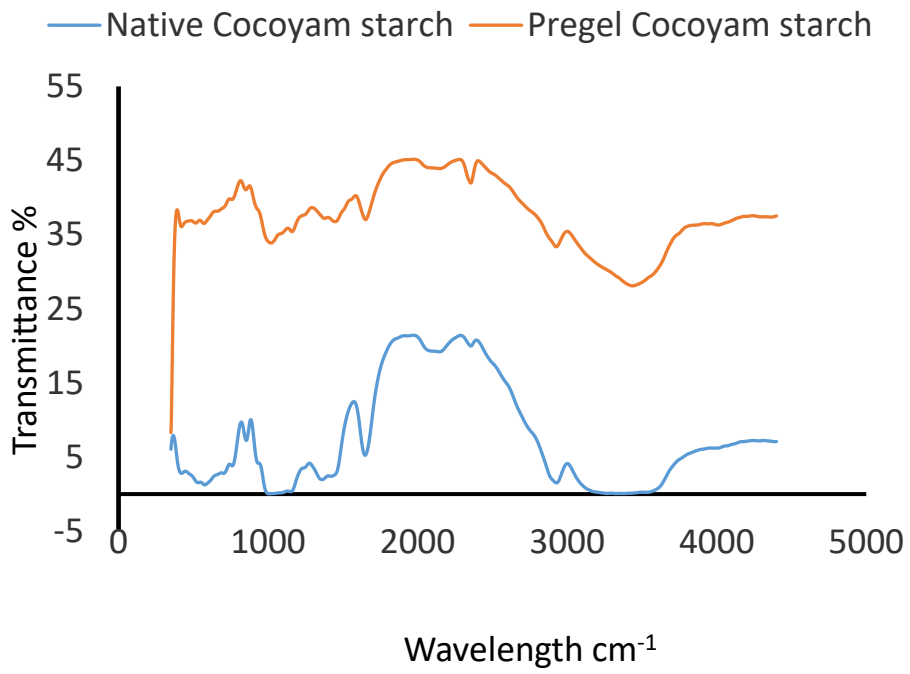


Figure 2: FTIR spectra of (a) native and (b) pregelatinized cocoyam starches

Table 1: Material and flow properties of native and pregelatinized cocoyam starches (mean ± sd, n = 3)

Cocoyam starch	Size µm	Swelling Index	Particle density (gcm^{-3})	Bulk density (gcm^{-3})	Tapped density (gcm^{-3})	Hausner's ratio	Carr's index (%)	Angle of repose (°)	Flow rate (g/s)
Native	6.24±1.79	0.52±0.00	1.424±0.01	0.448±0.76	0.682±1.00	1.52±0.17	34.31±0.17	67.66±0.20	0.05+0.00
Pregel	138.75±59.21	2.03±0.00	1.493±0.02	0.566±1.04	0.833±1.00	1.47±0.19	32.05±0.26	49.14±0.29	0.52±0.03

The results showed the particle, bulk and tapped densities of pregelatinized starch were greater than those of native starch. Particle density affects the packing behavior of materials during tableting, especially at the initial phase of compression. The higher values of the densities may be advantageous because of the reduction in the fill volume of the die during tableting (Nidal *et al*, 2015). The values of Hausner's ratio and Carr's index obtained for the starches as well as the angle of repose and flow rate are also presented in Table 1. Low values of Hausner's ratio is an indication of good powder flow. Native cocoyam starch had a higher Hausner's ratio than pregelatinized starch indicating that modification by pregelatinization improved flow. The Carr's index measures compressibility of a powder and provides an indirect measure of a material fluidity. The higher the value, the more cohesive is the powder indicating poor flow (Carr, 1965). The modified starch had a lower Carr's index suggesting improved flow. The angle of repose can be used to assess inter-particulate frictional forces operating within the powder system, measuring the resistance of the powder mass to flow. An angle of 30º or below indicates free flow while angle of 40º or above indicates poor flow. Results showed that modification of native starch by pregelatinization significantly reduced angle of repose, confirming improved flow properties. Flow rate of pregelatinized starch was also significantly higher than that of the native starch.

The values of the viscosity of the native and pregelatinized starches are presented in Table 2. The viscosity of a fluid is a measure of its resistance to gradual deformation by shear stress or tensile stress. The process of modification of native starch by pregelatinization reduced the viscosity significantly at both 50 and 100 rpm. With increased speed, the viscosity of starches increased but that of the pregelatinized starch was significantly lower.

Table 2: Viscosity profile of native and pre-gelatinized cocoyam starches (2%w/v)

Starch	Speed rpm	Viscosity (cP)	Torque (%)
Native	50	35.24	88.7
	100	64.0	3.3
Pregelatinized	50	16	0.3
	100	20	1.0

Material properties of the co-processed excipients

The scanning electron micrograph (SEM) and FTIR spectrum of the co-processed excipient are shown in Figures 3a and 3b respectively. The particles of the co-processed excipients formed larger aggregates with irregular shapes that showed mechanical interlocking of the particles of the starch and gum. The FTIR spectrum of the co-processed excipients showed retention of all the major peaks of individual polymers, showing absence of chemical interaction between the individual excipients during processing.

The values of the particle, bulk and tapped densities are presented in Table 3. Materials with low particle density at a given pressure would yield more cohesive compacts than those with higher values. This implies that the developed co-processed excipients would readily form tablets at lower compression pressure when compared to acacia gum alone. The flow properties of the co-processed excipients were determined using Hausner's ratio, Carr's index calculated from the bulk and tapped densities and these values as well as those of angle of repose and flow rate are presented in Table 3. Powder flow involves frictional contact of individual particles and such interparticulate friction has been demonstrated to have significant effects on powder packing (Zang *et al*, 2001). Higher Hausner's ratio values predict a significant densification of powders while lower values suggest better flow. Flow properties increased as the content of Cocoyam starch in the co-processed excipients increased. On the other hand, acacia gum had the highest values of Carr's index indicating good compressibility but poor flow. The values of angle of repose and flow rate also suggested that the co-processed excipients had improved flow when compared to acacia gum.

Angle of internal friction

Varthalis and Pilpel (1976) showed that the angle of internal friction would be more indicative of flow pattern than the angle of repose owing to its poor reproducibility. Therefore, the angle of internal friction of starches were obtained using the relationship existing between the porosity of the powder and the number of taps. The plots are presented in Figure 4. The values of the angle made between the ordinate line and the abscissa (angle of internal friction) are also presented in Table 3.

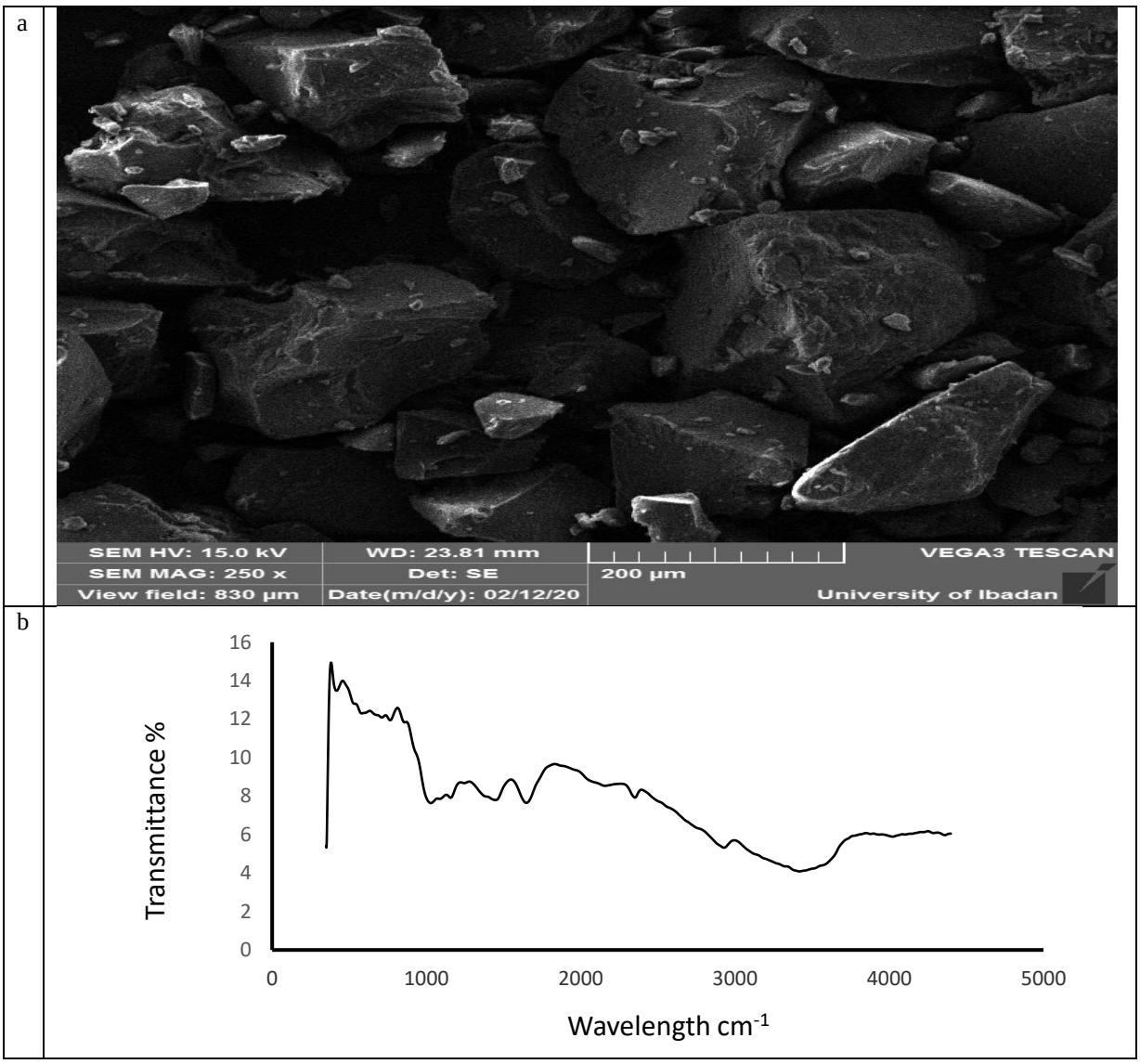


Figure 3: (a) SEM and (b) FTIR spectrum of co-processed excipient

Table 3: Densities and flow properties of co-processed excipients

Batch	Cocoyam: Acacia Gum	Particle density gcm^{-3}	Bulk density gcm^{-3}	Tapped density gcm^{-3}	Hausner's ratio	Carr's index %	Angle of repose °	Flow Rate g/s	Angle of internal friction °
B_1	100:0	1.493±0.02	0.516±0.05	0.628±0.00	1.22±0.08	17.83±0.23	51.90±0.06	0.53±0.03	19.31±2.00
B_2	97.5:2.5	1.341±0.07	0.512±0.06	0.628±0.03	1.21±0.08	18.03±0.23	53.13±0.06	0.56±0.01	44.90±3.06
B_3	95:5	1.364±0.12	0.523±0.05	0.638±0.00	1.22±0.08	18.17±0.24	56.94±0.06	0.55±0.02	44.63±4.40
B_4	92.5:7.5	1.426±0.01	0.519±0.05	0.651±0.00	1.25±0.09	20.28±0.23	59.25±0.06	0.54±0.02	46.63±2.25
B_5	90:10	1.413±0.00	0.526±0.05	0.651±0.00	1.24±0.09	19.20±0.24	58.82±0.05	0.53±0.02	46.53±1.66
B_6	85:15	1.392±0.08	0.519±0.05	0.634±0.01	1.23±0.08	18.44±0.24	56.94±0.06	0.48±0.03	46.62±3.06
B_7	80:20	1.394±0.07	0.519±0.04	0.628±0.17	1.24±0.08	18.36±0.24	58.36±0.06	0.47±0.01	44.90±1.55
B_8	0:100	1.349±0.01	0.508±0.05	0.655±0.00	1.29±0.10	22.44±0.22	65.30±0.10	0.26±0.01	45.78±0.99

Higher values of angles indicate greater cohesiveness. The higher values of the angle of internal friction in comparison to pregelatinized Cocoyam starch confirmed that the co-processed excipients had significantly better compressibility, imparted by the presence of acacia gum.

Compaction properties

The capacity of a material to form compact tablets with adequate tensile strength under the impact of densification is referred to as compactibility (Okore, 1999). A highly compactible powder enables particles to get closer to each other, thus facilitating interparticulate bonding and the formation of stronger compacts. Kawakita plots as well as plots of consolidation behavior are shown in Figures 5a and b respectively. From the two plots, the Kawakita parameters 'a' and 'b' and the consolidation index (C) and rate (K) were determined and the values are presented in Table 4. The coefficient of linearity of the plots are also presented in Table 4. Kawakita's equation relates the degree of volume reduction of a powder bed to the applied pressure under tapping. The linear relationship obtained suggest that the equation can be used to interpret the densification of the powders. The coefficient of linearity of the plots are also presented. The Kawakita 'a' refers to the minimum porosity of the powder bed before compression which is related to its compressibility and is obtained from the slope (Podzeck and Miah, 1996). The higher the 'a' value of the powder, the better the compressibility; an essential requirement in direct compression of tablets (Llic *et al*, 2009). The value of 'b' is an inverse measure of cohesiveness and is obtained from the intercept of the plot. The results shows that acacia gum had the highest value of 'a', hence its compressibility and ability to impart high mechanical strength in tablet formulations. The value of K, consolidation rate, is a measure of the rate of packing of powder granulation while C, consolidation index, is a measure of the effect of packing on flow. The higher the index, the higher is the flow. As the amount of Cocoyam starch in the co-processed excipients increased, there was an increase in the rate of consolidation and consolidation index, indicating that the co-processed excipients had enhanced flow properties as well as good packing. The consolidation behavior of the co-processed excipient is likely to affect the degree of consolidation of formulations containing these materials as filler-binder during compression.

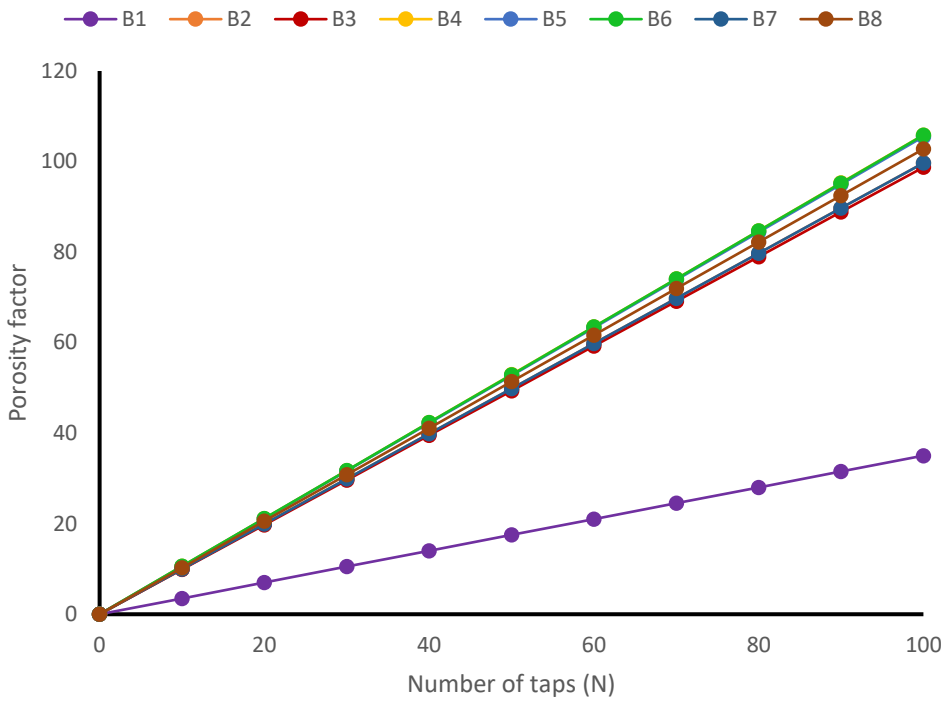


Figure 4: Plots of porosity factor as a function of number of taps (N) for the co-processed excipient

Table 4: Compaction properties of the batches of co-processed excipients

Batch	Cocoyam: Acacia gum	Kawakita parameters		Consolidation rate K	Consolidation index C	Coefficient of linearity r^2
		Compressibility (a)	Cohesiveness (b)			
B_1	100:0	0.189	0.133	0.1805	1.0905	0.9895
B_2	97.5:2.5	0.191	0.168	0.1221	0.9857	0.9742
B_3	95:5	0.190	0.148	0.2048	1.1449	0.9480
B_4	92.5:7.5	0.223	0.082	0.2347	1.1597	0.9867
B_5	90:10	0.206	0.113	0.2109	1.1269	0.9320
B_6	85:15	0.193	0.150	0.1615	1.0562	0.9680
B_7	80:20	0.191	0.076	0.2551	1.2642	0.9511
B_8	0:100	0.229	0.259	0.1042	0.8535	0.9644

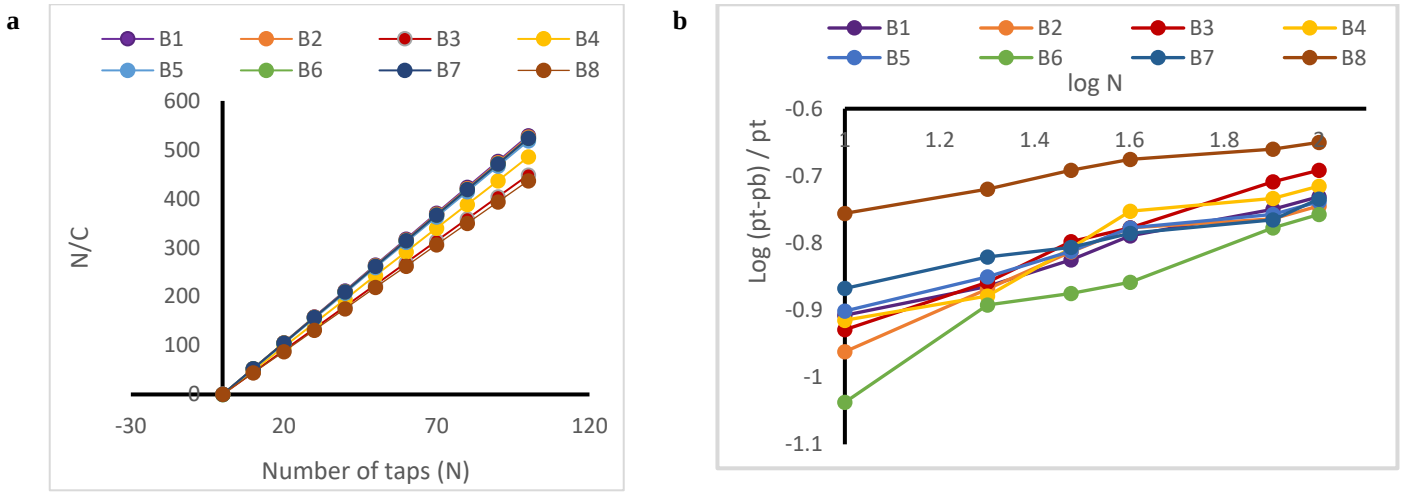


Figure 5: (a) Kawakita plots; (b) Plot of Log (ρ_T - ρ_B) / ρ_T vs Log N of the co-processed excipients

Tablet properties

Metoprolol tablets containing selected co-processed excipients B_2, B_4 and B_6 (Cocoyam: Acacia gum 97.5:2.5; 92.5:7.5, 85:15 respectively) and those containing pre-gelatinized cocoyam starch only (B_1) and acacia gum only (B_8) were formulated and evaluated for their tablet properties. The co-processed excipients were selected based on flowability and compressibility. The FTIR spectra of the pure drug, metoprolol succinate tablets containing co-processed excipients (crushed into powder) are presented in Figure 6. The FTIR analysis reveal that the integrity of metoprolol succinate was maintained with no chemical interaction between the co-processed excipients and the drug.

The values of tablets weight, thickness, crushing strength, friability, disintegration time and dissolution time of the tablets are presented in Table 5.

Tablet weight and thickness

The percentage weight variation and average thickness values of metoprolol tablets were within Pharmacopeia limits. The test for uniformity of weight is a simple way to assess variation in content of drug dose, which makes the test useful as a quality control procedure during tablet production. There was no significant variation in the weights and thickness of tablets produced by the co-processed excipients and individual excipients.

Mechanical properties

The mechanical strength of tablets is an important property and it plays a significant role in product development and manufacturing control. Tablet

friability is a measure of the ability of tablets to withstand stresses.. Tensile strength and hardness serve as the indicators of the strength of a compact (Pamar and Rane, 2009). The ranking of the friability was $B_1 = B_4 > B_2 > B_6 > B_8$. The tablets failed to meet Pharmacopeia specifications of ≤ 1% for uncoated tablets. The ranking of the crushing strength was $B_8 > B_4 > B_6 > B_2 > B_1$. Generally, tablets containing the co-processed excipients showed higher crushing strength and lower friability than those containing pregelatinized starch alone.

Release properties

Disintegration time

Disintegration time is the time it takes for a tablet dosage form to break into primary particles upon exposure to an appropriate medium. Disintegration tests are indirectly related to drug bioavailability and product performance. For conventional immediate release tablets, disintegration should not exceed 15 min

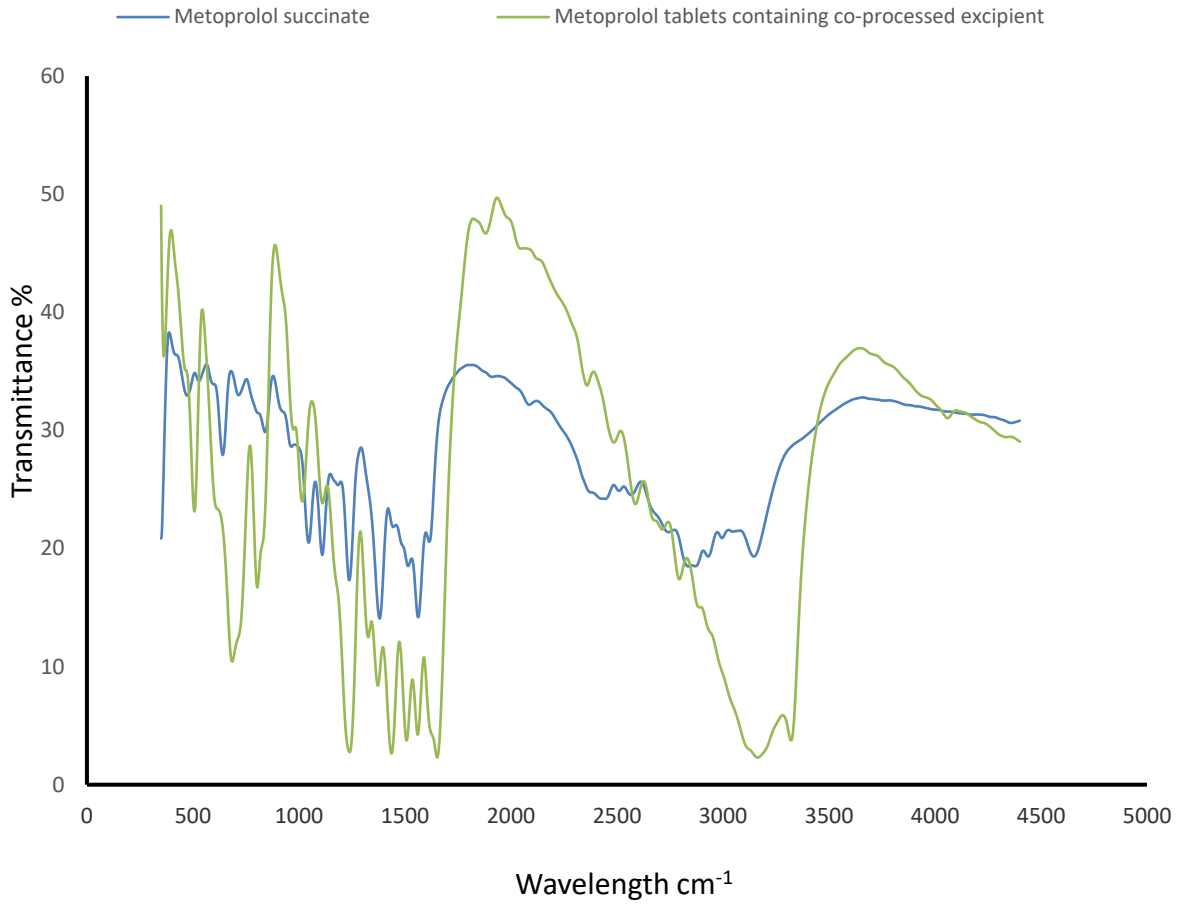


Figure 6: FTIR of pure metoprolol succinate and metoprolol succinate tablets containing the co-processed excipient

Table 5: Mechanical and release properties of metoprolol tablets (mean ± sd, n = 3)

Batch	Cocoyam : Acacia gum	Tablet Weight (g)	Tablet Thickness (mm)	Crushing Strength (MNm^{-2})	Friability (%)	Disintegration time (min)	t_{80} (min)
B_1	100:0	0.500 ± 0.02	0.50 ± 0.04	101.00 ± 13.00	2.47±0.05	1.25 ± 0.05	20.00
B_2	97.5:2.5	0.510 ± 0.03	0.51 ± 0.01	106.03 ± 15.80	2.03±0.07	1.80± 0.20	30.00
B_3	95:5	0.502 ± 0.01	0.52 ± 0.03	115.33 ± 12.40	2.06±0.07	1.41 ± 0.41	35.00
B_4	92.5:7.5	0.505 ± 0.02	0.47 ± 0.03	121.20 ± 7.70	2.06±0.08	1.47 ± 0.45	45.00
B_6	85:15	0.498 ± 0.01	0.50 ± 0.03	118.13 ± 5.40	1.61±0.06	5.75 ± 0.25	50.00
B_8	0:100	0.508 ± 0.03	0.49 ± 0.00	136.40 ± 8.70	1.24±0.08	13.89 ± 1.69	65.00

The ranking of the disintegration time was B_8> B_6 >B_2> B_4 >B_3> B_1. All the tablets produced passed the disintegration test with tablets containing the co-processed excipients disintegrating within 1.41 to 5.75 min. On the other hand, it took the tablets containing acacia gum alone over 13.89 min to disintegrate. The significant reduction in disintegration time of tablets containing the co-processed excipients may be attributed to the presence of pregelatinized starch with larger particles that created more pore channels that aided absorption of water into the matrix of tablets, thus, enhancing disintegration.

Assay of drug content

Assay of drug content revealed a range of 98.11±2.75 to 99.92±1.30 % of metoprolol succinate. This conforms to International Pharmacopoeia (IP) specifications for drug content of the tablet being 90 -110 % (IP, 2003).

Dissolution test

The dissolution plots are shown in Figure 7. From the dissolution plots, the time taken for 80 % drug release (t_{80}) was determined and the values of t_{80} are presented in Table 5. The ranking of t_{80} was B_8> B_6>B_4 > B_3 >B_2> B_1. From the results, it was observed that tablets containing the acacia gum alone had the highest dissolution time (> 60 min). This could be due to the formation of a dense matrix around the drug particles by acacia, providing more barriers that retarded drug particles escape during dissolution. The co-processed excipients imparted fast dissolution time on metoprolol succinate tablets, an important requirement in the use of metoprolol tablets for treatment of hypertension, angina pectoris, and arrhythmias. The results confirm the suitability of the co-processed excipients of Cocoyam starch and acacia gum as potential directly-compressible excipients for high mechanical strength and fast release of drugs in tablet formulations.

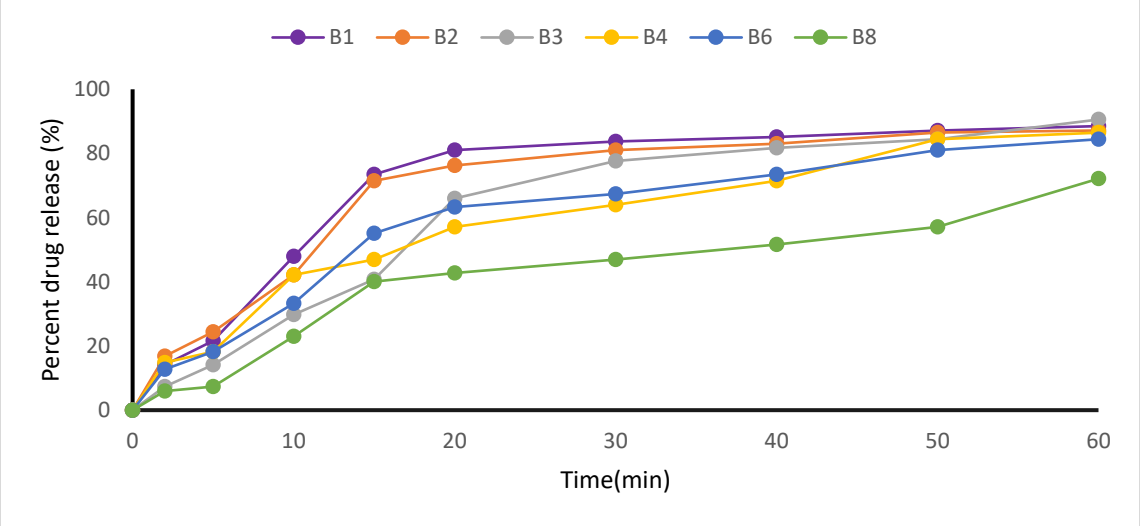


Figure 7: Dissolution profile of Metoprolol tablets containing pregelatinized Cocoyam starch (B_1), Acacia gum (B_8) and selected co-processed excipients (B_2, B_3, B_4 &B_6)

CONCLUSION

Co-processing of pregelatinized cocoyam starch with acacia gum produced new excipients with improved flow and compressibility when compared to the individual excipients. The co-processed excipients imparted higher crushing strength, lower friability, faster disintegration time and shorter dissolution time to metoprolol succinate tablets. The optimum formulation contained co-processed excipients of pregelatinized Cocoyam starch: acacia gum at ratio 97.5: 2.5. Pregelatinized Cocoyam starch is thus a suitable polymer in the formulation of co-processed excipients with acacia gum. The novel co-processed excipient would be useful as a directly-compressible excipient to overcome the challenges of individual ingredients in the formulation of tablets that require good mechanical strength and fast release.

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