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Powder, Compaction and Tableting Properties of Co-processed Silicified Starch

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Authors' contributions

This work was carried in collaboration between all authors. Author YEA designed the study and wrote the manuscript. Author JGM carried out the experiment and collected data from the study. Author OJO conducted the analysis of results and provided guidance for the entire study. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To evaluate the powder, compaction and tableting properties of co-processed silicified starch for direct compression formulation.
Study Design: The study was designed to co-process cassava starch and colloidal silicon dioxide in a combination ratio of 98:2 using a simple physical method.
Place and Duration of Study: Department of Pharmaceutics and Pharmaceutical Microbiology, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, between March 2013 and June 2013.
Methodology: Co-processing of cassava starch and colloidal silicon dioxide was carried out using the method of co-fusion where a dispersion of cassava starch was prepared in distilled water (40% w/w) and mixed with colloidal silicon dioxide prior to thermal treatment at a temperature of 54±2ºC for 15 min in a water bath. The co-processed mixture was dehydrated with ethanol (99%) and tray dried in a Hot air oven at 40ºC for 2 h. It was then kept in an air-tight container for further studies. Powder properties were assessed by measuring the angle of repose, bulk and tapped densities,

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Carr's index and Hausner's ratio. Compaction studies were carried out on tablets compressed at a range of pressures on the Hydraulic Carver Press and analyzed using Heckel and Kawakita equations. Tablets were prepared using chloroquine phosphate as the drug of choice on a Single Stroke Tablet Press by direct compression and evaluated under uniformity of weight, thickness, crushing strength, friability, disintegration and dissolution tests.
Results: The studies revealed an improvement in the functionality of the co-processed excipient with respect to flow, compression and tableting properties when compared to cassava starch.
Conclusion: The silicification of cassava starch by co-processing was able to improve the powder and compaction properties of the excipient suitable for producing tablets by direct compression.

Keywords: Cassava starch; colloidal silicon dioxide; co-processing; direct compression; tablet.

1. INTRODUCTION

The tablet is a solid dosage form in which the drug component is combined with a number of excipients to aid formulation of the desired product. These excipients include bulking agents, binders, disintegrants, lubricants, glidants and coatings, all of which have some function to aid processing of the drug substance into the end-product. The excipients and drug substance are processed through a series of unit operations such as mixing, blending, granulation, tableting and often coating to form the final product.

The final tablet has to fulfil a number of characteristics, including the ability to deliver an accurate dose of the drug into the patient's system at the required rate, as well as the physicochemical properties that make it easy to handle, administer and store. For dispensable products, these include a suitable size, hardness, texture and stability, as well as taste and smell. Over the years, three methods have been established in the preparation of tablets namely wet granulation, dry granulation and direct compression.

Direct compression is gaining popularity over other tablet manufacturing methods because of its simplicity involving fewer unit operations and utilizes much less energy, thereby reducing the overall cost of the process [1]. It is by far the easiest means of making tablets because it only involves the main steps of powder blending, lubrication and compression [2]. Suitable for moisture and heat sensitive active pharmaceutical ingredients (APIs), it presents few stability issues and involves a limited number of excipients.

The process of direct compression is highly influenced by the mechanical properties of the excipients used such as flow, compression and dilution potential, since about 70% of solid dosage formulations contain excipients at higher percentages than APIs [3,4]. Because there is no granulation step to improve flow and compaction, it is usually necessary to use excipients specifically designed for direct compression and engineered to provide the necessary flow and compaction properties [5,6].

In a bid to provide excipients suitable for direct compression, the strategy of co-processing has been introduced, gaining recognition over the years. Co-processing is a particle engineering technique based on the concept of excipient interaction at the sub-particle level involving two or more existing excipients. It provides a functional synergy of the interacting excipients as well as masking the undesirable properties of the individual components [6]. The aim of co-processing is to obtain a product with added value by a balance of its functionality and production costs.

Many researchers in the pharmaceutical industry have employed this technique to develop excipients with improved functionalities suitable for a wide spectrum of applications (7, 8 and 9). Three chitin metal silicates (CMS) prepared by co-processing were evaluated as a potential multifunctional single excipient in a study carried out by Hamid et al. [7]. The study yielded tablets with acceptable crushing strength. Novel co-processed chitin-mannitol (2:8, $^{w}/_{w}$) mixture prepared by wet granulation was found to be useful in the formulation of poorly compressible, high strength, and low strength active pharmaceutical ingredients [8] due to the inherent binding and disintegration properties of the co-processed mixture.

The novel SMCC II prepared by spray drying yielded more benefits in terms of functionality as compared with the parent cellulosic II material [9]. A new directly compressible co-precipitated powder composed of rice starch and colloidal

silicon dioxide prepared in an optimized ratio of 4:1 was found to exhibit superior flowability and compactibility when compared to native starch and the physical mixture [10].

A comprehensive review of literature has not reported the co-processing of cassava starch and silicon dioxide by co-fusion method. The study was therefore aimed at exploiting the benefits of co-processing by combining cassava starch and silicon dioxide in a ratio similar to Prosolv® (Silicified microcrystalline cellulose, 98:2) to impart functionality for direct compression. Starches have been used conventionally as an excipient in the formulation of tablets by wet granulation acting either as a binder and/or a disintegrant. However, it lacks the properties required for a robust direct compression hence, the need to co-process with silicon dioxide to improve functionality. Colloidal silicon dioxide is a compressibility enhancing material used as a glidant to facilitate the flow of powder blends during tableting.

The powder, compaction and tableting properties of the co-processed excipient was characterized and compared with Prosolv®.

2. MATERIALS AND METHODS

2.1 Materials

The materials used include colloidal silicon dioxide (CAB-O-SIL®, CABOT GmbH, Germany), Prosolv® SMCC HD 90 (JRS Pharma GmbH & Co. KG, Rosenberg, Germany), chloroquine phosphate (BDH Chemicals Ltd Poole, England). Cassava starch was extracted from tubers of *Manihot esculenta* in the process lab of the Department. All other materials and solvents used were of analytical grade.

2.2 Methods

2.2.1 Extraction of cassava starch

Cassava roots (*Manihot esculenta*) were freshly harvested from the International Institute for Tropical Agriculture (IITA) Farms, Shika, Zaria, and taken to the Department of Biological Sciences, Ahmadu Bello University, Zaria, for identification. It was given the voucher no: 900187. The method of Alebiowu [11] was adapted for the extraction of cassava starch. The cassava tubers were peeled, washed and cut into small pieces before soaking in distilled water for 24 h for softening. The softened tubers were milled to a pulp and the starch grains separated from the suspension using the wet sieving technique. The sediment obtained after settling from the suspension was centrifuged to obtain pure starch. The starch obtained was dried in a hot-air oven at 40ºC for 5 h and then stored in an air-tight container in preparation for further use.

2.2.2 Co-processing

Co-processing was carried out by a method described by Olowosulu et al. [12] with modifications. 100 g of a suspension containing 40% $^{w}/_{w}$ of cassava starch was prepared in a 500 mL beaker using 150 mL of distilled water. Silicon dioxide 2.04 g was weighed and dispersed in the starch slurry with constant stirring for 5 min prior to pregelatinization at 54±2ºC for 15 min in a water bath (HH-S Digital, Nigeria). The co-processed mixture was dehydrated with ethanol (99%), passed through a sieve (0.8 mm) and tray dried in a Hot air oven (Gallenkamp Oven BS, England) at 40ºC for 2 h. It was then kept in an air-tight container for further studies.

2.2.3 Powder characterization

2.2.3.1 Optical microscopy

Powder samples were mounted in glycerol on slides and observed under the microscope. Optical images of the samples were taken using a digital camera.

2.2.3.2 Angle of repose

Powder sample (50 g) was poured through a glass funnel at a height of 10 cm onto a level bench top. The height (h) and radius (r) of the conical heap formed were measured and the tangent of the angle of repose was calculated by the *h/r* ratio. A mean of three determinations was obtained (n=3).

2.2.3.3 Particle density, bulk and tapped densities, Hausner's ratio, Carr's index

The particle density was determined using a solvent pycnometric method with xylene as the displacement fluid. The bulk and tapped densities were determined as the ratio of powder weight to the powder volume before tapping and after tapping until volume was constant. Porosity (Ɛ) was calculated based on the particle density determined using solvent pycnometry. Hausner's ratio (HR) was calculated as the ratio of the bulk density to the tapped density, while Carr's index (CI) was the percentage ratio difference between

the values of the two densities to that of the tapped density. The equations for calculation are given below:

$$\text{Ɛ} = 1 - \frac{B_D}{\rho_T} \quad \text{CI} = \frac{T_D - B_D}{B_D} \times 100\ \% \quad \text{HR} = \frac{T_D}{B_D}$$

Where B_D, T_D and ρ_T are bulk density, tapped density and particle density respectively.

2.2.3.4 Swelling index (SI) and moisture content

5 g of the powder was poured into a 100 mL graduated cylinder and the initial bulk volume (V_1) was noted. The final volume (V_2) of the powder dispersed in water was recorded after 24 h of standing. The swelling index was calculated using the equation given below:

$$\text{SI} = \frac{V_2}{V_1}$$

Moisture content of the powder was determined by heating 2 g of the powder to constant weight at 105ºC in the Hot air oven (Gallenkamp Oven BS, England). The percentage moisture content was determined as follows:

% moisture content =

$$\frac{Initialweight - finalweight}{Initialweight} \times 100\ \%$$

2.2.4 FT-IR

The IR spectra of the physical mixture and the co-processed excipient were measured using the Fourier Transform Infrared Spectrometer (FTIR-8400S, Shimadzu, Japan). Each sample was pulverized, gently triturated with the KBr powder in a weight ratio of 1:100, and then compressed using a hydraulic press at a force of 10 T for 2 mins. The disc was then placed in the sample holder and scanned from 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1}.

2.2.5 Compaction studies

Compacts weighing 500 mg were compressed at pressures ranging from 28.3-283.1 MN/m^2 using a 12 mm punch and die set on a Hydraulic Carver Press (Carver Inc., USA). The die was lubricated with a dispersion of magnesium stearate in ethanol before each compression. A dwell time of 30 s was kept constant for each compression. The tablets were kept in a desiccator for 24 h to allow for elastic recovery. Tablet dimensions of weight and thickness were measured and the porosity, apparent and relative densities of compacts for each compression pressure was calculated using the formulas given below. A graph of ln (1/1-D) against P (Heckel plot) and P/C against P (Kawakita plot) were used to analyse the compaction profile.

Porosity (Ɛ) = $1 - D$

Apparent density (ρ_A) = $\frac{Weight(g)}{Volume(\pi r^2 h)}$

Relative density (D) = $\frac{\rho_A}{\rho_T}$

where *r* and *h* are the radius and thickness of the tablet respectively.

2.2.6 Tableting

Tablets containing chloroquine phosphate as the active drug were prepared by direct compression using the excipient as the sole ingredient. The tablet formula is given below in Table 1. Powder mixtures of the drug and excipient were compressed into tablets on a Single Stroke Tablet Press (Type EKO, GmbH, Germany). The tablets were stored for 24 h to allow for elastic recovery prior to evaluation of its properties.

2.2.7 Tablet characterization

The tablets formed were characterized by carrying out the following tests. Test for uniformity of weight was conducted on 20 tablets according to the method described by the USP. Tablet thickness was measured using the digital vernier calliper while the breaking force required to crush the tablet was determined using the tablet hardness tester (Monsanto Chemical Co., USA). Friability was measured using the friabilator (Type TA3R, Erweka, Germany) rotating at 25 rpm for 4 min. The disintegration test was performed on six [6] tablets using the disintegration tester (Type ZT3, Erweka, Germany) while *in vitro* dissolution studies was conducted using the dissolution apparatus (Type DT, Erweka, Germany). The dissolution medium used was distilled water and the apparatus was set to rotate at 100 rpm. 5 mL samples were withdrawn periodically and immediately replaced with 5 mL of distilled water after every withdrawal. The samples collected were filtered and suitably diluted with the dissolution medium before the absorbance readings were taken at a wavelength of 343 nm using the UV/VIS spectrophotometer (Thermo Fisher Scientific Inc., Cambridge, UK).

Table 1. Tablet formula

Ingredients	StarSil 50	Prosolv® 50	StarSil 40	Prosolv® 40
Chloroquine (50,60%)	250	250	250	250
StarSil (40,50%)	250	-	167	-
Prosolv® (40,50%)	-	250	-	167
Mag. Stearate (0.5%)	2.5	2.5	2.1	2.1
Total (mg)	502.5	502.5	419.1	419.1

3. RESULTS AND DISCUSSION

The physical features of CS and StarSil in terms of particle size and shape were carefully observed under the optical microscope at 40 x and 100 x magnifications. The images captured are presented as Fig. 1. Both powders appeared spherical under view. However, some irregular shaped particles were noticed in the image of StarSil which is most likely to be that of colloidal silicon dioxide (CSD). Particle size remained unchanged after co-processing probably due to the surface activity of colloidal silicon dioxide. Based on the spherical shape observed for StarSil, it is expected to flow freely.

The physico-mechanical properties of CS, StarSil and Prosolv® are given in Table 2. Angle of repose was measured by determining the angle formed when the powder was poured at an angle of 45º into a glass funnel to form a conical pile of powder on a level bench top. The results obtained range from 22-36º with Star Sil having the least angle of 23.3º. This indicates that powder flow improved after co-processing with colloidal silicon dioxide as a result of the reduction in the interparticulate friction due to enhanced sphericity of particles after coating with silicon dioxide. As a rule, values less than 30º are considered to be suitable for solid dosage form technology [13]. Powder flow is critical to the success of the direct compression process.

There was also a corresponding increase in flow rate of cassava starch when processed with silicon dioxide compared to cassava starch alone. CI and HR parameters were computed from the values of bulk and tapped densities and the results obtained are consistent with an improvement in powder flow. There was a significant difference in the values obtained for cassava starch and StarSil. As a rule, HR values ≤1.2 and CI values ranging between 5-12% correspond to a free-flowing powder [14]. The decrease in bulk density observed after co-processing is closely related to a decrease in cohesivity of the powder which translates to a greater tendency for improved flow of the powder [14]. This was well correlated with an increase in powder porosity of StarSil due to its less dense packing behavior resulting in more pore spaces existing between particles of StarSil. Particle density also decreased slightly after co-processing suggesting that cassava starch is denser than StarSil. The presence of silicon dioxide on the surface of cassava starch may have contributed to the decrease in particle density due to the creation of more pore spaces in the particle structure of cassava starch. Moisture content values ranged from 7-11% with StarSil having a moisture content of 8.5% which was less than that of cassava starch after drying. The moisture present in StarSil may have enhanced powder flow by lubricating the particles and possibly prevents, to some degree, the cold welding of asperities thereby reducing the frictional forces that oppose motion [15]. It is necessary to optimize the moisture content because it has a bearing on the flow properties of the material and also determines the chemical and physical stability of the formulation [15]. Swelling index increased marginally with co-processing arising from the increased uptake of water through the porous channels created by the presence of silicon dioxide.

Fig. 2 shows the IR spectra for StarSil, its physical mixture, chloroquine (CQ) and StarSil-CQ mixture. The spectra for StarSil and its physical mixture did not show any significant change in position of the absorption bands. This indicates that there was no chemical change arising as a result of co-processing. The changes observed in the behavior of the material can be ascribed to modification in the physical properties. Similarly, IR scan of drug and excipient blend did not reveal any major shift in the absorption bands suggesting that the drug chosen for the study is compatible with the excipient.

Heckel and Kawakita equations were used to analyze the compaction data. The plots are presented as Fig. 3. Out-of-die analysis was used to obtain measurements for Heckel and Kawakita plots. The parameters derived from the

plots are given in Table 3. The Heckel model describes the densification events occurring in a powder bed when pressure is applied [16]. The yield pressure value (P_Y), which is the inverse of the slope of the linear portion of the Heckel curve, refers to the pressure at which the material begins to deform plastically. Compared to Prosolv, the yield pressure of StarSil was lower, suggesting that the onset of deformation of StarSil was faster and less resistant to densification. Both materials had a yield pressure above 100 MPa, indicating that the mode of deformation was more brittle than plastic [17]. This has been attributed to the presence of colloidal silicon dioxide in both materials which increases the brittle behavior during consolidation (18). The D_0 represents the initial densification of the powder bed occurring as a result of die filling. The values obtained for both materials were comparable. The D_B parameter represents the extent of powder bed arrangement due to particle fragmentation/ rearrangement at low pressures. The values obtained indicate that Prosolv® had a higher fragmenting ability compared to StarSil. The fibrous shape of Prosolv® may have contributed significantly to its high fragmenting ability due to its ability to accommodate or bend at low pressures [18]. The total degree of densification occurring in a powder bed (D_A) for Prosolv® was more than that of StarSil owing to its fibrous morphology.

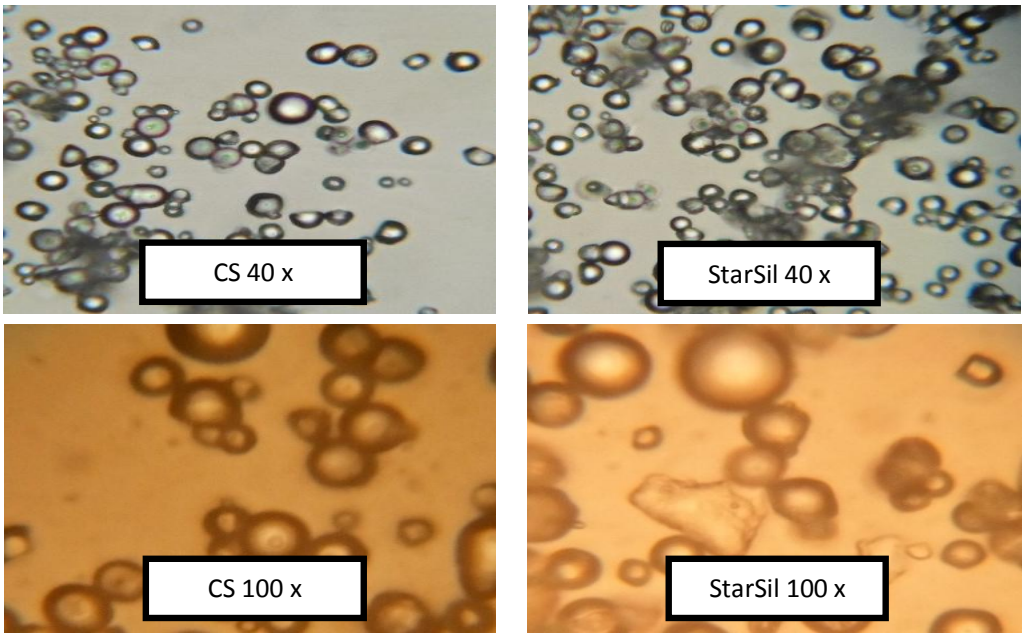

Fig. 1. Photomicrographs of CS and StarSil

Table 2. Physico-mechanical properties of CS, StarSil and Prosolv®

Properties	Cassava starch	StarSil	Prosolv®
Angle of repose (°)	36.0±5.6	23.3±3.1	22.0±0.5
Flow rate (g/s)	3.9±0.5	4.5±0.1	5.3±0.2
Bulk density (g/mL)	0.63±0.0	0.5±0.0	0.47±0.02
Tapped density (g/mL)	0.98±0.04	0.57±0.0	0.52±0.005
Porosity (%)	56	64	64
Carr's index (%)	36	12	11
Hausner's ratio	1.6	1.14	1.12
Particle density (g/mL)	1.43	1.38	1.31
Moisture content (%)	11	8.5	7
Swelling capacity	1.05	1.45	1.07

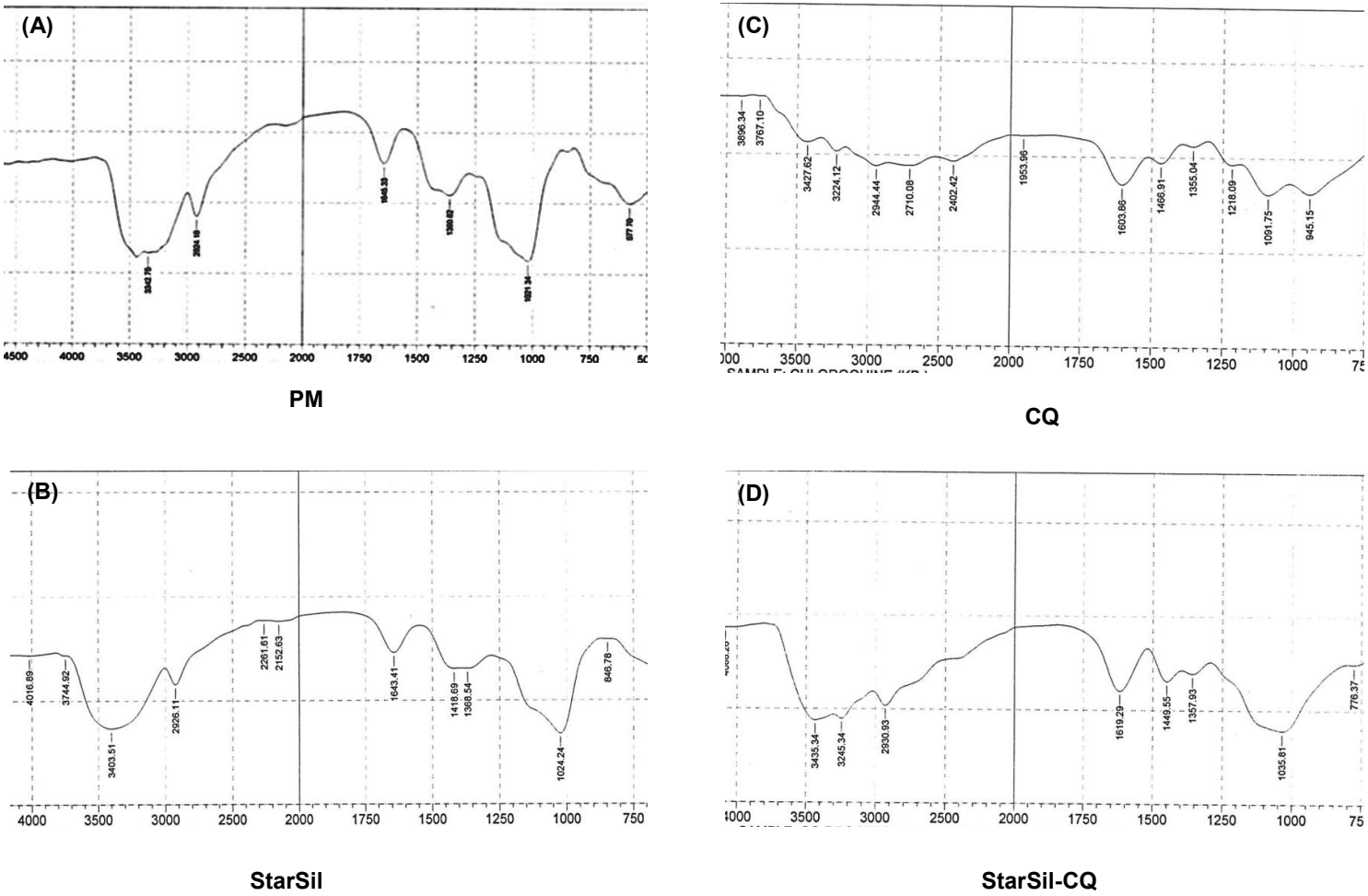

Fig. 1. FT-IR spectra of (A) PM, (B) StarSil, (C) CQ, and (D) StarSil-CQ

The Kawakita equation was used to describe the relationship between the degree of volume reduction of the powder column and the applied pressure [19]. The parameters are given in Table 3. Constant '*a*', describes the compressibility or the degree of densification due to compression, and is equal to the minimum porosity of the bed prior to compression. The D_I value obtained from the Kawakita analysis represents the initial relative density with the application of low pressure. There was no much difference in the degree of packing exhibited by the two materials in terms of the '*a*' parameter. The D_I values obtained for both materials were relatively same. The pressure required to reduce the volume of the powder bed by 50% denoted by P_K was slightly higher for StarSil suggesting its greater resistance to deformation than Prosolv®. This implies therefore that Prosolv® had a greater degree of plasticity as compared to StarSil. P_K values are an inverse measure of the amount of plastic deformation occurring during compression and are calculated from the reciprocal of the '*b*' parameter.

The physical properties of the tablets prepared by direct compression were evaluated and the results are presented in Table 4. Tablets containing StarSil performed better in terms of weight uniformity and disintegration time. Tablets of StarSil disintegrated in less than 5 min owing to the presence of colloidal silicon dioxide which enhanced water uptake to facilitate disintegration. The breaking force required to crush Prosolv® tablets was higher compared to StarSil with a corresponding decrease in the friability. This may have been due to the higher degree of plastic deformation occurring in Prosolv® during compaction that ensures stronger tablets are formed. The *in vitro* drug release studies (Fig. 4.) conducted for both materials revealed that only about 50% of the drug was released after 45 min. The high crushing strength recorded for both materials may have affected the rate of drug release from the tablet.

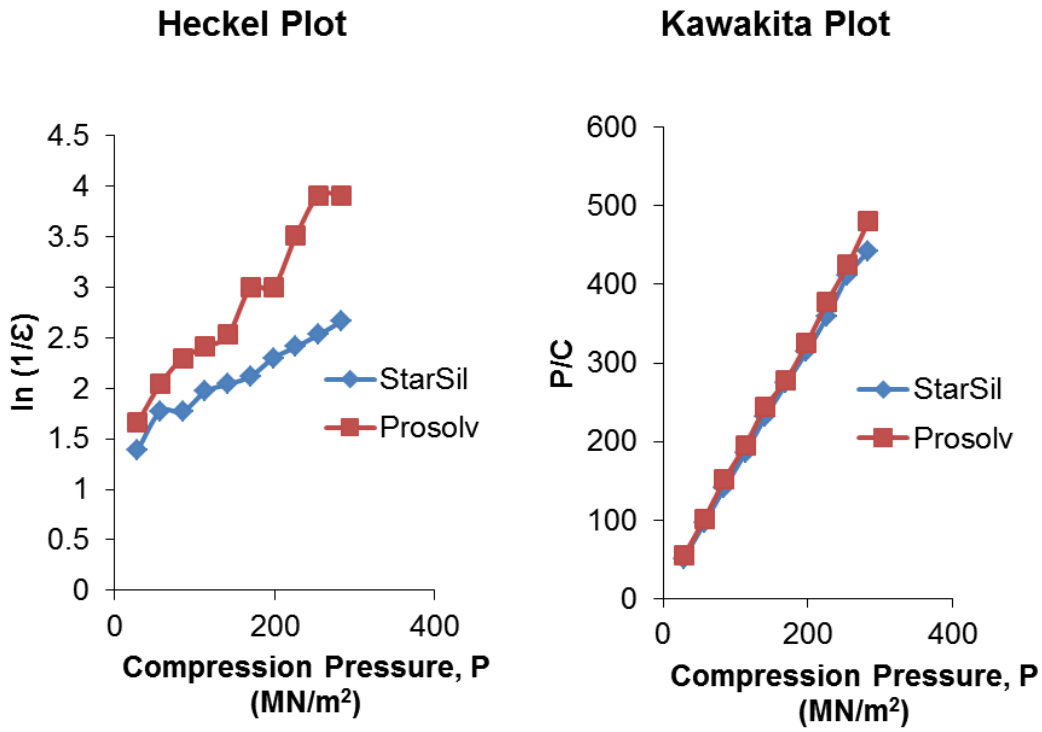

Fig. 2. Heckel and kawakita plots

Table 3. Heckel and Kawakita parameters

Heckel parameters						Kawakita parameters				
	P_Y	D_0	D_A	D_B	R^2	*a*	*b*	P_K	$D_I(1-a)$	R^2
StarSil	209.94	0.362	0.750	0.387	0.928	0.644	0.172	5.815	0.355	0.999
Prosolv®	246.53	0.358	0.858	0.499	0.999	0.610	0.197	5.075	0.389	0.998

Table 4. Tablet properties

Properties	Prosolv® 50	StarSil 50	Prosolv® 40	StarSil 40
Weight uniformity (mg)	477±18.2	475±23	439±7.1	411±4.5
Disintegration time (min)	17.43±2.4	4.36±0.09	9.93±1.2	3.1±0.1
Crushing strength (N)	138±4.5	132±8.4	140±0	98±8.4
Friability (%)	0.61	0.82	0.3	0.75
Thickness (mm)	2.88±0.06	3.08±0.06	2.52±0.26	2.68±0.28

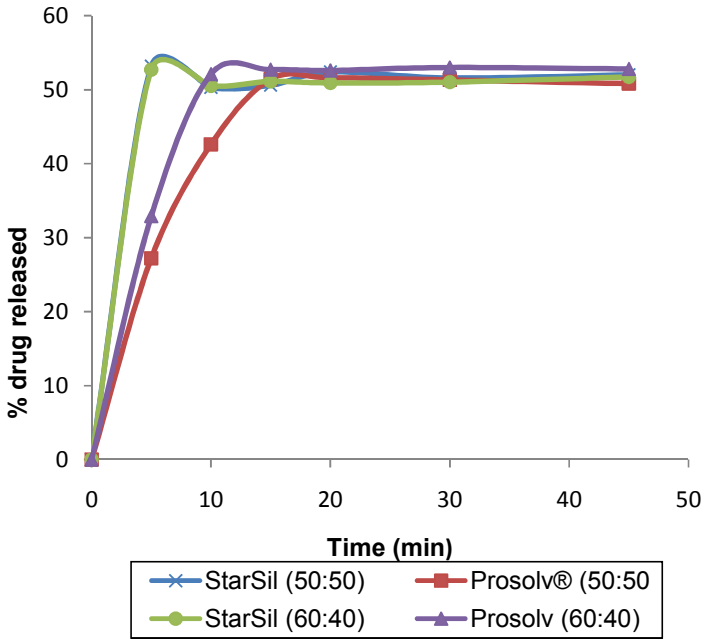

Fig. 3. Dissolution plot

4. CONCLUSION

The findings from this study have revealed that co-processing of cassava starch with 2% colloidal silicon dioxide improved the functionality of starch for direct compression. Better flow and compaction properties were obtained relative to the native starch. The excipients used for co-processing were compatible and maintained their chemical properties even after co-processing. The developed excipient was also compatible with the drug used in the formulation. The tablets produced with this excipient met the USP requirements and compared well with the Prosolv® counterpart.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Bolhius GK, Chowhan ZT. Materials for direct compaction. In: Alderborn G, Nystrom C, editors. Pharmaceutical powder compaction technology.New York: Marcel Dekker Inc; 1996.
2. Bansal AK, Nachaegari SK. Co-processed excipients for solid dosage forms. Pharm Technol. 2004;52-64.
3. Jacob S, Shirwaikar AA, Joseph A, Srinivasan KK. Novel co-processed excipients of mannitol and microcrystalline cellulose for preparing fast dissolving tablets for Glipizide. Indian J Pharm Sci. 2007;69(5):633-639.
4. Kibbe AH, editor. Handbook of Pharmaceutical Excipients. London: Pharmaceutical Press; 2000.
5. Hiestand EN. Mechanics and physical principles for powders and compacts. West Lafayette, Indiana, U.S.: SSCI Inc; 2003.
6. Block LH, Moreton RC, Apte PS, Wendt RH, Munson EJ, Creekmore JR, Persuad IV, Sheehan C, Wang H, Co-processed excipients. Pharmacopoeial Forum. 2009;35:1026-1028.
7. Hamid RAS, Al-Akay F, Shubair M, Rashid I, Al Remawi M, Badwan A, Evaluation of three chitin metal silicate co-precipitates as a potential multifunctional single excipient in tablet formulations, Marine Drugs. 2010;8:1699-1715.
8. Daraghmeh N, Rashid I, Al Omari MMH, Leharne SA, Chowdhry BZ, Badwan A. Preparation and Characterization of a novel co-processed excipient of chitin and crystalline mannitol. AAPS Pharm Sci Tech. 2010;11(4):1558-1571.
9. Rojas J, Kumar V. Comparative evaluation of silicified microcrystalline cellulose II as a direct compression vehicle. Int J Pharm. 2011;416:120-128.
10. Kittipongpatana PS, Kittipongpatana N. Preparation and physicomechanical properties of co-precipitated rice starch-colloidal silicon dioxide. Powder Technology. 2012;217:377-382.
11. Alebiowu G. Steeping period influence on physical, compressional and mechanical properties of tapioca starch. J Pharm Res. 2007;6:139-144.
12. Olowosulu AK, Oyi A, Isah AB, Ibrahim MA. Formulation and evaluation of novel coprocessed excipients of Maize Starch and Acacia Gum (StarAc) for direct compression tableting. Int J Pharm Res Innov. 2011;2:39-45.
13. Zhou Q, Armstrong B, Larson I, Stewart PJ, Morton DA. Improving powder flow properties of a cohesive lactose monohydrate powder by intensive mechanical dry coating. J Pharm Sci. 2010;99:969-981.
14. Patel S, Kaushal AM, Bansal AK. Compression physics in the formulation development of tablets. Crit Rev Ther Drug Carr Sys. 2006;23(1):1-65.
15. Nokhodchi A. An overview of the effect of moisture on compaction and compression. Pharm Technol. 2005;46-66.
16. Heckel RW. Density-pressure relationship in powder compaction. Trans Metal Soc AIME. 1961;221:671-675.
17. York P. Crystal engineering and particle design for the powder compaction process. Drug DevInd Pharm. 1992;18:677-721.
18. Rojas J, Kumar V. Comparative evaluation of silicified microcrystalline cellulose II as a direct compression vehicle. Int J Pharm. 2011;416:120-128.
19. Kawakita K, Ludde KH. Some considerations on powder compression equations. Powder Technol. 1971;4:61-68.

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