ORIGINAL RESEARCH

Evaluation of the disintegrant property of co-processed sorghum starch-silicon dioxide excipient in chlorpheniramine orodispersible tablets

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ABSTRACT

Background: Fast dissolving or orodispersible tablets are highly desirable in groups such as children, uncooperative, nauseated, or those on reduced water intake to ease the difficulties associated with swallowing the conventional solid dosage forms.
Objectives: The work aimed to evaluate the disintegrant property of sorghum starch-silicon dioxide co-processed mixture in the formulation of chlorpheniramine orodispersible tablets.
Method: Different batches of orodispersible tablets of chlorpheniramine maleate (4 mg) were prepared by direct compression method using Avicel® as a bulking agent and four different types of disintegrants (sorghum starch, co-processed sorghum starch-colloidal silicon dioxide, sodium starch glycolate and croscarmellose sodium) at varying concentrations (5, 10 and 20 %). The formulated tablets were subjected to weight variation test, thickness, crushing strength, friability test, wetting time, water absorption ratio, disintegration test and *in-vitro* dissolution study.
Results: For tablets above 250 mg, it is expected that not more than two tablets should deviate from the average weight by 5% and none should deviate by more than 10%, all the formulations yielded tablets within this specification. The disintegration time of tablets containing 10% of disintegrants was all less than 60 s except those containing sorghum starch (SS) which took a long time. Similarly, the time taken to release 50 % of the drug ($t_{50\%}$) for tablets containing 10% sorghum starch was 25 s, 5 s for tablets containing 10% sorghum starch-colloidal silicon dioxide excipient and 8 s for tablets containing 10% of either croscarmellose sodium or sodium starch glycolate. The differential scanning calorimetry study results suggested that the drug and the excipient are compatible.
Conclusion: The results show that sorghum starch-silicon dioxide co-processed mixture can be used as an alternative to croscarmellose sodium and sodium starch glycolate in orodispersible tablet formulations.

Keywords: disintegrant, co-processing, chlorpheniramine, orodispersible tablets, sorghum starch

INTRODUCTION

Oral administration of drugs is preferred as a result of accurate dose delivery, low cost of therapy, non-invasive method of delivery and the relative ease of administration leading to a high level of patient compliance[1]. Tablets and capsules constitute the largest proportion of oral

dosage forms that are currently employed; they are usually administered with a glass of water to aid their disintegration process. Some physiological and neurological conditions associated with aging like difficulty in swallowing (dysphagia), hand tremors or risk of choking sometimes make the utilization of the conventional tablets and capsules inconvenient or unfeasible. Swallowing difficulties in geriatrics, paediatrics, patience on reduced water intake or among individuals with little or no access to water (e.g. travellers) makes conventional solid dosage forms difficult to use conveniently[3,4.] To solve this problem, orodispersible tablets were developed. Orodispersible tablets are dosage forms that dissolve rapidly when placed into the oral cavity without the addition of extra water. Upon the administration of an orodispersible tablet, the active ingredient dissolves or disperses in the saliva which is then absorbed into the blood circulation after swallowing[5]. The United States Food and Drug Administration Center for Drug Evaluation and Research (CDER)[6], defines an orally disintegrating tablet as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". The European Pharmacopoeia[7], similarly describes orally disintegrating tablets as 'uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed', and gives a time limit of disintegration as 3 minutes. Orally disintegrating tablets are also referred to as orodispersible, mouth dissolving, rapidly disintegrating, fast melt, and quick dissolve system[8]. The aim of this study was to evaluate the disintegrant property of sorghum starch-silicon dioxide co-processed mixture in the formulation of chlorpheniramine fast dissolving tablets

MATERIALS AND METHODS

Materials

Colloidal silicon dioxide (Cab-O-Sil®, M5-DP, Cabot GmbH, Germany), Chlorpheniramine maleate (Sigma Aldrich, USA), Croscarmellose sodium (Vivasol®, JRS Pharma, Germany), Sodium starch glycolate (Primojel®, DFE Pharma, Germany), Avicel® PH 101(BDH Chem. Ltd Poole, England), Talc, (BDH chem. Ltd Poole, England), Aspartame, (BDH chem. Ltd Poole, England), Magnesium Stearate, (BDH chem. Ltd Poole, England), Sorghum starch and co-processed sorghum starch-silicon dioxide excipient (batches A1 and B1 respectively) were obtained from batches processed in our laboratory. All other reagents and solvents were analytical grade and were used as supplied.

Methods

Preparation of chlorpheniramine maleate orodispersible tablet by direct compression method using different disintegrants

Twelve different formulations of orodispersible tablets of chlorpheniramine maleate (4 mg) were prepared by direct compression method using Avicel® as a bulking agent and four different types of disintegrants (sorghum starch, co-processed sorghum starch-colloidal silicon dioxide, sodium starch glycolate and croscarmellose sodium) at varying concentrations (5, 10 and 20 %) as demonstrated in table 1. Mannitol was added to mask any unacceptable taste while magnesium stearate and talc were added as lubricant and glidant respectively. All the ingredients were passed through a sieve size 250 µm and mixed by tumbling method (powders were transferred into a 1000 ml amber coloured glass bottle covered with an appropriate closure to prevent leakage while mixing) for 15 min, except talc and magnesium stearate which were added later and was further mixed for 2-3 min. The resulting powder mixture was compressed into tablets using the manual single punch tableting machine (AR 400 Erweka Apparatus GmbH, Germany) fixed with a 12 mm flat circular punch. The target tablet weight was 400 mg. The formulated tablets were then properly labelled and stored in a desiccator for 24 h before further testing.

Table 1: Formulation design for fast dissolving tablets of chlorpheniramine maleate containing varying concentrations of disintegrants

Ingredients (mg)	Formulation											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
CHP	4	4	4	4	4	4	4	4	4	4	4	4
SS	20	40	80	-	-	-	-	-	-	-	-	-
SSC	-	-	-	20	40	80	-	-	-	-	-	-
SSG	-	-	-	-	-	-	20	40	80	-	-	-
CM	-	-	-	-	-	-	-	-	-	20	40	80
TALC	4	4	4	4	4	4	4	4	4	4	4	4
MS	2	2	2	2	2	2	2	2	2	2	2	2
MT	6	6	6	6	6	6	6	6	6	6	6	6
AV	364	344	304	364	344	304	364	344	304	364	344	304
TOTAL	400	400	400	400	400	400	400	400	400	400	400	400

Chlorpheniramine (CHP), Sorghum starch (SS), Sorghum starch-colloidal silicon dioxide co-processed excipient (SSC), Sodium starch glycolate (SSG), Croscarmellose sodium (CM), Magnesium stearate (MS), Mannitol (MT), Avicel (AV)

Evaluation of tablet properties

Weight variation test

Twenty tablets were selected and weighed on an electronic balance and the average weight was determined. Then individual tablets were weighed, and the individual weight was compared with the average weight[9].

Tablet diameter

Six tablets were examined for their diameter using Vernier calipers and the mean diameter value (± S.D) was calculated and reported.

Crushing Strength

Ten tablets from each batch of formulation were weighed individually on a Mettler balance (Type 163, Mettler instruments A.G Switzerland). From the mean tablet weight, the deviation of each tablet from the mean weight was calculated and the standard deviation determined[10].

Friability test

Ten tablets were randomly picked from each batch, brushed carefully and lightly until all surface powder was removed and then weighed (W1). They were then placed inside the Erweka (TA 3R Germany) friabilator and operated or rotated 100 times in 4 min i.e. 25 revolutions per minute, removed dusted and reweighed (W2). The loss in the weight of tablets is the measure of friability and is expressed in percentage as given in equation 1[5]

$$\text{Percentage friability} = \frac{W_1 - W_2}{W_1} \text{ X } 100 \quad \ldots 1$$

Wetting time

Five circular tissue papers of 10 cm diameter were placed in a petri dish with a 10 cm diameter. Ten millilitres of water-containing Eosin, a water-soluble dye, was added to a petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablet was noted as the wetting time[11].

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A tablet was placed on the paper (*Wb*) and the time required for complete wetting was measured. The wetted tablet was then weighed (*Wa*). The water absorption ratio (R), was determined[12] using equation 2.

$$Water\ absorption\ ratio = \frac{Wa-}{Wb} \text{ x } 100 \quad \ldots 2$$

Where *Wb* is the weight of the tablet before water absorption and *Wa* is the weight of the tablet after water absorption.

Disintegration test

The time required for six tablets per batch to disintegrate was determined using Erweka disintegration tester (ZT Erweka, Germany) containing distilled water thermostatically maintained at 37± 2 °C as the disintegration medium. The disintegration apparatus was calibrated to operate at thirty cycles per minute. The time taken for the tablet or its fragment to pass through the mesh into the disintegration medium was recorded. The mean of three determinations was calculated to be the disintegration time[5].

Since super disintegrants are usually used in solid dosage forms at concentrations not exceeding 10 %, based on the data obtained from the disintegration time test, formulations containing 10 % disintegrant concentration (F2, F5, F8 and F11) were selected (being the maximum acceptable concentration that yielded the optimal disintegration time across the formulations) for further studies[13].

Dissolution time test

In vitro dissolution studies of the prepared chlorpheniramine maleate tablets were carried out in 900 ml of 0.1N HCl as the dissolution medium using USP XXI type II (Paddle method). The test apparatus was set at an agitation speed of 50 rpm and the temperature was maintained constantly at 37 ± 0.5 °C. Then 5 mL aliquots were withdrawn at time intervals of 0, 10, 20, 30 sec, 1, 2, 5, 10, 15 and 20 min. The withdrawn sample was replaced with 5 ml of fresh dissolution medium each time and analyzed at λmax of 265 nm using a spectrophotometer (Shimadzu Corporation Model 1700, Japan). The dissolution experiment was conducted in triplicate[5].

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) windows version 23 (SPSS Inc., CA, USA). The results were presented descriptively in tables and charts. The differences between the data sets were determined using T-test and $p < 0.05$ was considered statistically significant.

RESULTS

The physical properties of the fast-dissolving chlorpheniramine tablets are as presented in Table 2. The crushing strength of the tablets was in the range of 2.0 to 5.0 kgf. All the formulations except sorghum starch-based formulations (F1, F2 and F3) and F7 had a weight loss of less than 3 % during the friability test. No tablet deviated by more than the maximum standard deviation of 5%.

Formulations containing SSC, CM and SSG exhibited an increase in both wetting time and water absorption ratio, the reverse was however observed in formulations containing SS. As expected, the disintegration time was observed to have decreased with an increase in the concentration of disintegrant in formulations containing SSC and SS, however, there was an increase in the disintegration time of formulations containing CM and SSG, with increasing disintegrant concentration.

The release profiles of the optimal formulations (F2, F5, F8 and F11) are presented in Figure 1. The time taken to release 50 % of the drug ($t_{50\%}$) was less than 10 s for tablets containing SSC, CM or SSG, whereas, it took 25 s for the formulation containing SS. Also, the time taken for 80 % drug release ($t_{80\%}$) was in the order of SSC<CM<SSG<SS. The results of dissolution rates are presented in Table 3.

The DSC thermogram of chlorpheniramine (A), sorghum starch (B), sorghum starch co-processed excipient (C) and sorghum starch co-processed excipient plus chlorpheniramine (D) is presented in Figure 2. The DSC thermogram showed the presence of the drug within the excipient mix with no formation of newer peaks.

Table 2: Physical properties of the formulated fast-dissolving chlorpheniramine tablets

Formulation	Weight variation (mg)	Diameter (mm)	Crushing strength (kgF)	Friability (%)	Wetting time (seconds)	Water absorption ratio (%)	Disintegration time (seconds)
F1	407±4.40	12.06±0.15	2.2±0.10	11.81	32±0.05	114.29±0.03	560±1.00
F2	405±4.23	12.12±0.08	2.0±0.08	29.88	29±0.07	123.40±0.04	412±0.04
F3	408±3.87	12.14±0.06	2.7±0.04	4.39	26±0.02	112.64±0.01	104±0.02
F4	397±4.96	12.08±0.16	3.0±0.05	1.90	20±0.23	123.75±0.96	77±0.57
F5	401±4.55	12.07±0.13	3.0±0.07	1.80	28±0.04	142.19±0.80	40±0.60
F6	413±3.97	12.09±0.12	3.2±0.03	1.20	35±0.06	161.36±0.07	31±0.02
F7	401±4.00	12.09±0.06	2.8±0.13	3.22	22±0.03	237.10±0.03	17±0.01
F8	409±3.23	12.09±0.04	3.7±0.11	1.95	29±0.04	269.10±0.04	19±0.02
F9	413±4.14	12.10±0.02	5.0±0.06	1.45	80±0.01	293.95±0.05	48±0.02
F10	395±4.10	12.09±0.05	3.9±0.21	2.52	20±0.05	276.30±0.04	15±0.01
F11	400±3.78	12.08±0.04	3.8±0.11	2.01	25±0.03	380.45±0.05	16±0.03
F12	411±3.68	12.09±0.02	5.0±0.04	2.19	43±0.02	482.90±0.02	21±0.02

F1-F3: Sorghum Starch, F4-F6: Sorghum Starch Coprocessed, F7-F9: Croscarmellose Sodium, F10-F12: Sodium Starch Glycolate, Values presented as Mean ± S.D.

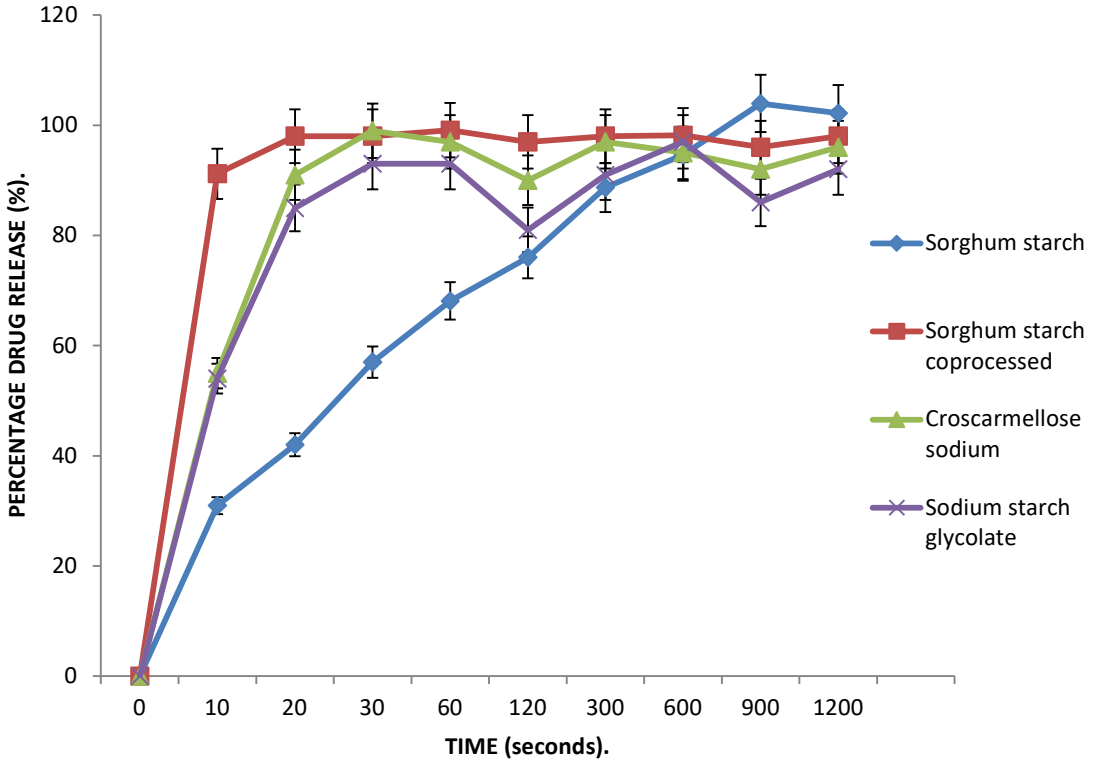

Figure 1: Release profiles of chlorpheniramine from optimized sorghum starch, sorghum starch co-processed excipient, croscarmellose sodium and sodium starch glycolate containing formulations

Table 3: Dissolution release time of chlorpheniramine from optimized SS, SSC, CM and SSG containing formulations

Formulation	Disintegrant	$t_{50\%}$ (Sec)	$t_{80\%}$ (Sec)
F2	SS	25	210
F5	SSC	5	8
F8	CM	8	17
F11	SSG	8	18

Key: Sorghum starch (SS), Sorghum starch-colloidal silicon dioxide co-processed excipient (SSC), Sodium starch glycolate (SSG), Croscarmellose sodium (CM)

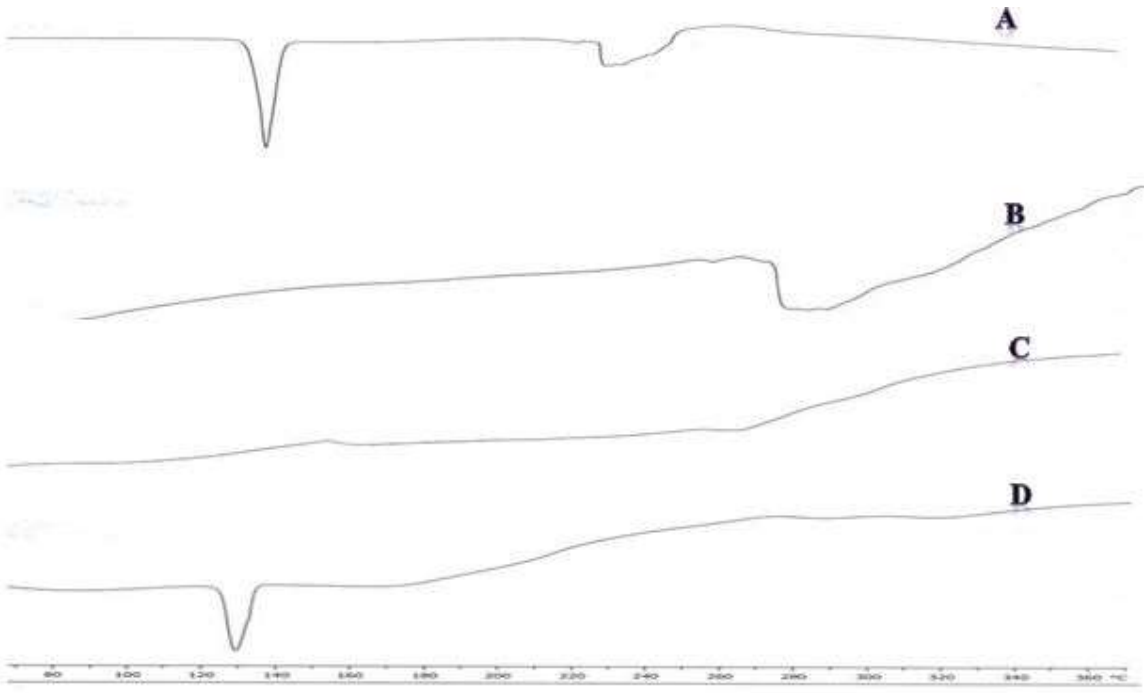

Figure 2: DSC thermogram of chlorpheniramine (A), sorghum starch (B), sorghum starch co-processed excipient (C) and sorghum starch co-processed excipient plus chlorpheniramine (D)

DISCUSSION

Co-processing of excipients is a technique that has been employed by many researchers in the pharmaceutical industries to develop excipients with improved functionalities suitability for a wide spectrum of applications[14]. The main objective of this was to explore the suitability of sorghum starch-silicon dioxide co-processed mixture in the formulation of chlorpheniramine fast-dissolving tablets. The results obtained from the uniformity of weight investigations conformed to the requirement of the British

Pharmacopoeia[15]. For tablets above 250 mg, the British Pharmacopoeia[15] states that not more than two tablets should deviate from the average weight by 5% and none should deviate by more than 10%. The test for uniformity of weight is a simple way to assess variation in drug dose, unacceptably high variations will reduce the content uniformity of medicines[16]. All the formulations yielded tablets which exhibited uniformity of weight values within the acceptable official limit.

Friability is a measure of the ability of tablet to withstand abrasion in handling, packaging, and shipment[17]. The obtained results show that formulation containing SS gave the highest percentage values while those containing SSC had the lowest values; this indicates particle compactness on the application of pressure. A maximum weight loss of not more than 1% is generally considered acceptable for most products[15]. Orally disintegrating tablets that are intended for immediate drug release are made to be soft and porous to facilitate fast disintegration and drug release. The formulations all had friability values greater than 1%. Similar findings have been reported[18]. Philip and Julita[19] stated that friability values in the range of 0 to 3% can be considered acceptable when using a direct compression method. Most of the formulations gave friability values within this range. Usually, most orodispersible tablets are packaged in aluminium blister packs, first, to provide additional protection to the near fragile nature of the tablet and secondly, to protect the product from environmental conditions such as humidity and temperature due to their hygroscopic nature[5].

Wetting time is the time taken for water to penetrate from the bottom to the topmost part of the tablet[20]. It is one of the vital parameters used to predict how much of the fluid is enough for breaking the tablet when placed upon the tongue. Short wetting time indicates a short disintegration time of the tablet.

The obtained results showed that formulations containing SSC (F4, F5 and F6) had a better wetting time in comparison to SS containing formulation (F1, F1 and F3). This can be attributed to the improved hydration capacity, moisture sorption and porosity properties after co-processing with colloidal silicon dioxide which led to higher capillary effect due to its hydrophilic highly porous nature[21]. All except the sorghum starch containing formulations exhibited decreased in wetting time with increase disintegrant concentration, this may not be unconnected to the higher hydrophilic nature and hydration capacity of all the other disintegrants compared to the sorghum starch[22,23].

The water absorption ratio also showed similar improvement for formulations containing SSC compared to those containing SS. This may also be attributed to the improved hydration capacity of the excipient as a consequence of co-processing with the highly hydrophilic colloidal silicon dioxide. Starches are known to be hygroscopic in nature, therefore, water retention within its matrix is known to occur as it swells, with CM and SSG known to swell up to 8 times its size (Raymond 2009), this explains why the absorption ratio is in the order SS<SSC<CM<SSG. The result also shows that the improvement is dependent on the amount of disintegrant used. Similar findings have been reported[24].

For the medicinal agent in a tablet to become fully available for absorption, the tablet must first disintegrate and discharge the drug to the body fluids for absorption. The British Pharmacopoeia[15] specifies that orodispersible tablets should disintegrate within 3 min. All the formulations passed this test except those containing 5 and 10% sorghum starch (F1 and F2), this may be due to the sorghum starch poor hydration capacity (compared to the other super disintegrants) leading to poor swelling, which is the mechanism by which starch is believed to exert its disintegrant property. The results indicate that co-processing

sorghum starch with colloidal silicon dioxide has led to its improvement as a disintegrant, this may be as a result of improved wicking effect (hydration capacity), improved absorption (swelling capacity) and capillary effect (porosity) all leading to a better tablet rupture time comparable with SSG and CM (known standards) containing formulations. Similar results have been reported[24,25]. However, for SSG and CM containing formulations, it can be seen that increasing the disintegrant concentration results in an increase in the disintegration time. Raymond[26] and Swatantra[27] reported similarly that at higher concentration, super disintegrant gels by forming a thick viscous barrier that retards disintegration. SSC and SS containing formulations however showed a decrease in disintegration time with an increase in disintegrant concentration. This result agrees with other findings[28].

Comparative evaluation of the release profiles showed that SSC, CM and SSG containing formulation gave comparable release rate, with 50% of the drug been released within 5 min (by SSC based tablets) and 8 min for CM and SSG containing tablets. All the formulations except F2, which contains sorghum starch, satisfied the FDA requirement, which specifies that a minimum 85% of the active substance in orodispersible tablets should be dissolved within 30 min[29,30]. The low release rate of SS containing formulation may not be unconnected to the poor hydration and swelling capacity of sorghum starch thereby impacting negatively on the dissolution time. The tendency of gel formation by the super disintegrants at higher concentrations might have slightly retarded the disintegration time and eventually impacted negatively on the release rate of its formulations (F8 and F11), thereby resulting in F5 showing slightly higher release rate.

The possibility of any interaction between the co-processed excipient and chlorpheniramine was studied by differential scanning calorimetry. There was no observable alteration in peak area, appearance of new peaks or elongation/broadening of an exo- or endothermic change, suggesting that the drug and the excipient are compatible[31].

CONCLUSION

The results show that sorghum starch-silicon dioxide co-processed mixture, when used in formulating chlorpheniramine orodispersible tablets, exhibit comparable property with croscarmellose sodium and sodium starch glycolate. Tablets formulated with the co-processed excipient exhibited acceptable characteristics, rapid disintegration and dissolution of the drug. The excipient can, therefore, be used as an alternative to croscarmellose sodium and sodium starch glycolate in orodispersible tablet formulations.

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