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A novel multifunctional pharmaceutical excipient: Modification of the permeability of starch by processing with magnesium silicate

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ABSTRACT

A directly compressible excipient has been developed by co-processing starch with magnesium silicate. The foregoing was achieved either by co-precipitation of magnesium silicate onto different types of starch or by dry granulation of maize starch with magnesium silicate. A variety of techniques (permeability, water retention/swelling, compression analysis, scanning electron microscopy, tensile strength and disintegration/dissolution studies) were used to characterize these systems. The permeability of the formulations produced using the two methods was evaluated experimentally using Darcy's permeability law. Magnesium silicate, as an anti-adhering agent, increases the permeability of both maize and partially pregelatinized starch, resulting in compacts of high mechanical strength, short disintegration time and low lubricant sensitivity. Such advantages are evident when the properties of the physical mixture of maize starch with magnesium silicate are compared with the co-precipitation and dry granulation techniques. Formulation with this novel excipient system, using paracetamol as a model drug, indicated its suitability as a single multifunctional excipient.

1. Introduction

Amongst a myriad of applications (Fredriksson et al., 1998), starch and its derivatives are widely used in the pharmaceutical industry due to their biodegradability and biocompatibility. Starch-based tablets (Kottke et al., 1992), capsules (Vilivalam et al., 2000), film coatings (Cummings et al., 1996; Milojevic et al., 1996), microspheres (Mundargi et al., 2008), subcutaneous implants (Désévaux et al., 2002) have all been exploited/utilized. Starch is one of the most widely used excipients in pharmaceutical formulations where it can be used both as a disintegrant and as a binder depending on the specific attributes necessary for the formulation (Cunningham, 1999). As a disintegrant, the mechanism of action of starch includes wicking–the imbibitions of water into the tablet matrix via capillary action. The subsequent interaction between water and starch granules leads to stress relaxation. Stresses in tabletted formulations arise from deformation caused by the application of compression forces in order to manufacture the tabletted form (Ferrari et al., 1996). Stress-release is responsible for the disruption of hydrogen bonds formed during compression. The concentration of starch used is crucial; if it is below the optimum concentration then there are insufficient channels for capillary action and if it is above the optimum concentration then it is difficult to compress the compacts (Kuttke and Rudnic, 2002). As a binding agent in tablet formulations, starch is heated in solution enhancing its conversion into a paste before addition to the formula powder blend (Subhadhirasakul et al., 2001). This process is referred to as "starch pasting" or "gelatinization" whereby a substantial change in both the chemical and the physical nature of granular starch takes place.

Gelatinization of starch plays an important role in the design of modified starch excipients with a wide range of properties ranging from compactable disintegrants to compactable excipients with sustained release properties (Herman et al., 1989a,b; Sanchez et al., 1995; Alebiowu and Itiola, 2002; Alebiowu and Itiola, 2003). Partially pregelatinized starches (e.g. starch 1500®) are effective disintegrants but they are not superdisintegrants and typically need to be used at high concentrations in order to obtain the required disintegration properties (Leach et al., 1959). Practically, they can be used up to concentrations that do not exceed 15–20% (w/w) to maintain disintegration and binding properties in tablet formulations. Furthermore, modified or unmodified starch excipients are generally characterized by their sensitivity towards lubrication. For example, magnesium stearate causes deleterious effects on the compactibility of tablets formulated with maize starch and starch® 1500 (Bos et al., 1987; St-Onge et al., 2005).

In summary, with regard to the use of starch products as multifunctional excipients, there exist a number of shortcomings and/or restrictions that have generated concentration limitations

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of starch in tablet formulations. These limitations – either directly or indirectly – affect disintegration time, drug release, tablet tensile strength and sensitivity towards lubrication for immediate release solid dosage formulations using either modified or unmodified starches.

Recently, progress in developing new excipients with multifunctional capabilities (as glidants, fillers, binders, and disintegrants) has exploited the use of magnesium silicate produced synthetically by co-precipitation (Rashid et al., 2009; Badwan et al., 2007). Incorporation of Mg silicate with defined pharmaceutical excipients, has beneficially resulted in compacts of high mechanical strength, that possess good compressibility characteristics and short disintegration times (Rashid et al., 2009) as well as low sensitivity towards lubrication (Rashid et al., 2010). Thus Mg silicate/starch preparations have the potential to fulfill the requirements of a multifunctional excipient. In this context the physical properties of compacts produced (disintegration time, tensile strength, powder compressibility), and sensitivity towards lubrication need to be investigated. On this basis, the current study reports the application of Mg silicate as an effective tabletting aid when used with maize starch granules using two techniques: (1) co-precipitation of Mg silicate onto a suspension of starch and (2) dry granulation of the native maize starch with Mg silicate using a roller compactor. Darcy's law is used to assess the permeability parameter of different types of native and modified starches and the role of Mg silicate in changing this parameter. Characterization of all the sample powders investigated was carried out using powder swelling capacity measurements, compression properties, morphology of the processed powders, and magnesium stearate lubricant sensitivity. The maize starch/Mg silicate excipient system was formulated with paracetamol as a model drug to assess its ability as a single multifunctional excipient and the dissolution profile is compared with that of the same model drug formulated using commercially available partially pregelatinized and fully pregelatinized starch excipients.

2. Methods

2.1. Materials

Commercial maize starch (Beijing Quanfeng Starch Company, China), cassava, potato, and rice starch granules (Bob's Red Mill, Milwaukie, OR, USA), starch 1500® (partially pregelatinized starch from Colorcon Limited, Dartford, Kent, UK) and Lycatab® PGS (fully pregelatinized starch, Roquette Freres, Lestrem, France) were used. The moisture content of maize starch was determined by drying in an air-oven at 105 °C for 24 h, and the average value found to be 9.1 ± 0.2% (w/w). Other reagents and materials used were: $Na_2SiO_3{\cdot}9H_2O$ (MW = 284.25, RANKEM, RFCL limited, New Delhi, India), $MgCl_2{\cdot}6H_2O$ (MW = 128.305, SIGMA Chemical Co., St. Louis, MO, USA) and paracetamol (Sri Krishna Pharmaceutical Ltd., Hyderabad, India).

2.2. Preparation of Mg silicate co-precipitate

250 mg of $Na_2SiO_3{\cdot}9H_2O$ was dissolved in 1 L of deionized water. A stoichiometric amount of $MgCl_2{\cdot}6H_2O$ (113 mg) was then gradually added to the Na silicate solution, according to the following reaction:

$$MgCl_2{\cdot}6H_2O + Na_2SiO_3{\cdot}9H_2O \rightarrow MgSiO_3 + 2NaCl + 15H_2O$$

The pH of the final suspension of Mg silicate co-precipitate was ~8.0 ± 0.1. After stirring for 10 min, the suspension was filtered using 20–25 μm filter paper (ALBET 135, Quantitative, Barcelona, Spain) and washed extensively with deionized water to remove the NaCl. The wet cake of Mg silicate retained on the filter paper was dried in an oven at 90 °C for 5 h.

2.3. Preparation of starch-Mg silicate co-precipitate

22 g of maize starch was suspended and stirred for 15 min in solutions of different concentrations of Na silicate at a Na silicate/water value of 1.72 g/mL (refer to the first three columns of Table 1). The aforementioned concentration of Na silicate represents the maximum allowable value for partial pregelatinization of starch to take place. Above this value complete gelatinization takes place, and is avoided in this study. The fraction of Na silicate in the formulation was calculated as the initial amount of Na silicate (dry basis) divided by the sum of the initial amounts of starch (dry basis) and Na silicate (dry basis) solids added to the mixture. To these partially pregelatinized starch suspensions $MgCl_2{\cdot}6H_2O$ powder was slowly added to stoichiometrically react with Na silicate in order to produce the suspended particles of the Mg silicate co-precipitated inside the starch suspension (Table 1). The pH of the final suspension of starch-Mg silicate co-precipitate was ~8.0 ± 0.1. The starch-Mg silicate suspensions were filtered, washed, and dried at 60 °C for 5 h. The fraction of Mg silicate was calculated as the stoichiometric amount of Mg silicate produced by the reaction of Na silicate with Mg chloride divided by the total amount of maize starch and Mg silicate present in the system (Table 1). The suspension was filtered using 20–25 μm filter paper and dried in an oven at 60 °C for 5 h. 500 g of the starch-Mg silicate co-precipitate samples at each concentration of Mg silicate were prepared.

2.4. Preparation of starch-Mg silicate by physical mixing and dry granulation

Mg silicate powder was physically mixed with native maize starch at the Mg silicate concentrations listed in the last column of Table 1. Mixing was carried out for 15 min at 25 rpm in a cubic blender connected to an Erweka multipurpose motor (Erweka AR400, Erweka GmbH, Heusenstamm, Germany). 100 g of each of the mixtures was prepared and divided into two portions (50 g each). The first portion was used as the physical mixture of starch with Mg silicate and the second was used for dry granulation. The second portion was subjected to compaction at a roll force of 1.4 t (metric ton) and a roll speed of 0.2 rpm using a lab scale roller compactor (TFC-LAB Micro Roller Compactor, Vector Corporation, IA, USA). The compacted powder flakes were crushed between two driven rollers running in opposing directions using an Erweka crushing accessory (ERW-TG2000) connected to the Erweka AR400 multipurpose motor. The resulting granules were passed through a 90 μm mesh sieve and collected on a 50 μm mesh sieve and used for further experimental work.

2.5. Analysis of powder permeability

In fluid dynamics, Darcy's law is a phenomenologically derived constitutive equation that describes the flow of a fluid through a porous medium (Stauffer, 2006). Darcy's law quantitatively describes one-dimensional water flow in a saturated medium, and can be stated as:

$$J = -K_S i \quad (1)$$

where J is water flux (or flow of water), K_S is the saturated hydraulic conductivity, and i is the hydraulic gradient. The minus sign keeps the right hand side of the equation positive – since the hydraulic gradient is formally and necessarily negative; the hydraulic gradient always decreases in the direction of water flow. For simplicity, the minus sign is subsumed into the i term in the remaining discussion.

Table 1
Composition of starch metal silicates used (in the presence of 22 g of maize starch).

Mass of Na silicate (hydrous) (g)	Volume needed to suspend maize starch (mL)	%, w/w Na silicate	Mass of $MgCl_2 \cdot 6H_2O$ (g)	Mass of magnesium silicate (calculated stoichiometrically) (g)	%, w/w Mg silicate
3	80	6.05	1.35	1.06	5.03
10	267	17.67	4.51	3.53	15.00
20	534	30.04	9.02	7.06	26.10
30	801	39.18	13.54	10.60	34.63
60	1600	56.30	27.08	21.20	51.45
100	2700	68.22	45.14	35.32	63.85
140	3740	75.04	63.20	49.44	71.20
250	6670	84.29	112.84	88.30	81.53

J can also be defined as:

$$J = \frac{Q}{At} \tag{2}$$

where Q is the quantity of water moving through a cross-sectional area (A) per unit of time (t). Flux is commonly expressed on a volume basis (e.g., m^3/m^2 s), which simplifies to a velocity term (m/s). This flux term, which is sometimes termed the specific discharge, is not the distance water travels per unit time as the units suggests. The reason for this is that A represents the cross-sectional area of the sample through which water flows. Water, of course, can only flow through the contiguous pore spaces. The average linear velocity of water is obtained by dividing J by the porosity of the sample. The original units represent volume (quantity) discharged (i.e., collected and measured) through a cross-sectional area per unit time. The effectiveness of the driving force behind water movement is described by i and is defined as:

$$i = \frac{\Delta h}{l} \tag{3}$$

where Δh is the difference in hydraulic head between the inflow and outflow of water and l is the length of the saturated sample medium. Furthermore, the hydraulic head represents the medium water potential. The hydraulic gradient is the difference in hydraulic head per unit distance. Solving Darcy's law for K_S yields:

$$K_S = \frac{J}{i} \tag{4}$$

K_S can be expressed using various units. The units and dimensions depend on those that are used to measure the hydraulic gradient (mass, volume, or weight) and flux (mass or volume); Δh maybe expressed on a pressure basis. However, for a homogeneous medium it simplifies to centimeters of head, and the hydraulic gradient (i) becomes unitless (e.g., cm/cm). Then, K_S has the same units as flux (m/s) or (length/time). Permeability is a synonym for K_S and is used as such hereafter.

In order to perform the permeability experiments, 10 g of the powder was added to a 50 cm transparent Biorad tube (Econo-Column, Hercules, CA, USA), with a porous polymer bed support at the bottom of the column to retain fine particles. The tube was equipped with an end cap at the bottom to stop or allow the discharge of water. Deionized water was added up to 40 cm from the perforated base and represents the height of the water head (i). The internal diameter of the tube was 2.4 cm. The tube containing the immersed powder was manually shaken in a clockwise/anticlockwise direction to allow complete saturation of the powder with water. The powder was allowed to sediment under gravity for a period of between 1 and 6 hr depending on the type of powder tested. The thickness (l) of the settled powder bed was recorded. When the end cap was removed, the first few turbid drops were returned back to the hydraulic head. When the outlet water became clear, the volumetric discharge rate of water was recorded taking into consideration that the hydraulic head must be continuously compensated with water in order to maintain a constant pressure (ΔH). Permeability was then calculated using Eq. (4).

Permeability tests were initially carried out on starch samples obtained from different plants [maize (MS), cassava (CS), potato (PS), and rice (RS)] and on modified starches: starch 1500® and Lycatab® PGS) and then repeated using all of the aforementioned native and modified starch types physically mixed with 30% (w/w) Mg silicate. All of the starch samples, with or without Mg silicate, were passed through a 20 μm mesh and collected on a 10 μm mesh (FRITSCH sieves, Fritsch Gmbh, Idar-Oberstein, Germany) prior to permeability testing. Five samples of each type of preparation were used for each permeability experiment. Furthermore, permeability tests were conducted on the starch-Mg silicate samples produced by co-precipitation, dry granulation as well as the physical mixture of starch and Mg silicate. The powders were passed through a 90 μm mesh sieve and collected on a 50 μm mesh sieve.

2.6. *Water retention of the tested powders*

5.0 g of each of the samples of starch-Mg silicate produced by co-precipitation, dry granulation, and physical mixing of starch-Mg silicate were quantitatively transferred into test tubes and weighed (w_1). 10.0 mL of deionized water was added and mixed for 30 s (Fisher Vortex Genie 2TM mixers, Pittsburgh, PA, USA). The samples were then allowed to stand at $25 \pm 2\,^{\circ}C$ for 20 min, centrifuged (2000 rpm, 15 min) and drained for 10 min at an angle of 10–15° to the horizontal. The test tubes were weighed (w_2) and the percentage water retained was calculated as follows: % water retained = $((w_2 - w_1)/w_1) \times 100$. The particle size range of the samples tested was 50–90 μm. Five samples of each powder were used for the water retention results.

2.7. *Swelling of sample powders*

10 g of maize starch was poured into a graduated cylinder. 20 mL of deionized water was added to the powder bed, mixed for 30 s, and the new volume of swelled starch was recorded (V_1). The volume of the saturated powder was recorded (V_2). The increase or decrease in volume was compared with the initial volume of maize starch (V_1), used as a reference, and calculated as $((V_2 - V_1)/V_1) \times 100\%$. The same test was performed on starch-Mg silicate produced by co-precipitation, the physical mixture of starch Mg silicate, and the starch-Mg silicate produced by dry granulation. The samples tested displayed a particle size range of 50–90 μm. Five samples from each type were used to assay the extent of swelling.

2.8. *Acquisition and analysis of compression data*

The Kawakita equation was employed to study powder compression and using the degree of volume reduction, C, a parameter equivalent to the engineering strain of the particle bed and is

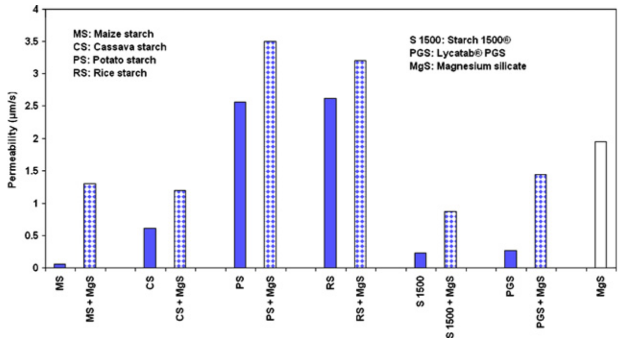

Fig. 1. Permeability of native and commercially modified starch samples (10 g) unprocessed or processed with 30% (w/w) Mg silicate by physical mixing, with a particle size of 10–20 μm.

expressed (Kawakita and Ludde, 1971) as:

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \tag{5}$$

or rearranged in linear form as:

$$C = \left[\frac{V_0 - V}{V_0}\right] = \frac{abP}{1 + bP} \tag{6}$$

where V_0 is the initial volume of the powder bed and V is the powder volume after compression; a and b are constants which are obtained from the slope and intercept of the P/C versus P plots, respectively. The constant a is equal to the minimum porosity of the bed prior to compression whilst the b term, the compression coefficient, reflects the plasticity of the material. Values of $1 - a$ yield the initial relative density of the material which have been shown to provide a measure of the packed initial relative density of tablets by the application of low pressure or what may be referred to as tapping (Odeku et al., 2005). The reciprocal of b yields a pressure term, which is the pressure required to reduce the powder bed by 50% and also provides an inverse measurement of plastic deformation during the compression process. The lower the value of $1/b$, the higher the degree of plastic deformation occurring during compression (Adams and McKeown, 1996).

Starch-Mg silicate co-precipitate (at a Mg silicate concentration of 15.00%, w/w), Mg silicate, and two samples of starch-Mg silicate produced by dry granulation at starch concentrations of 20 and 80% (w/w) were separately compressed by direct compression using a universal testing machine (UTM, RKM 50, PR-F system, ABS Instruments Pvt., Ltd., Leipzig, Germany). The particle size range of the compressed materials were unified by passing them through a 90 μm mesh and then collected on a 50 μm mesh. For tablet preparation, the punch speed was fixed at 10 mm/min. Different compression pressures from 10 to 70 MPa were applied. Three tablets were prepared to ensure reproducibility; the tablets were flat, 12 mm in diameter and 400 mg in weight. Bulk density was determined using a weighed 100 mL cylinder and a volumeter (Erweka GmbH, Heusenstamm, Germany). 20 g of the powder was gently filled into the cylinder. Bulk volume was read and bulk density calculated, as the average of five measurements. The average slope and intercept values of three preparations of the powders tested were ascertained.

2.9. Scanning electron microscopy

Samples of maize starch, starch-Mg silicate produced by co-precipitation or by dry granulation (both at a Mg silicate content of 15.0%, w/w) were each mounted on aluminum stubs and then coated with gold by sputtering at 1200 V and 20 mA for 105 s using a vacuum coater. Samples were examined using a FEI Quanta 200 3D SEM (FEI, Eindhoven, Netherlands).

2.10. Tensile strength and disintegration time testing

The tensile strength and disintegration time were tested for the powder samples of starch-Mg silicate produced by co-precipitation and by dry granulation techniques in addition to the physical mixture of maize starch and Mg silicate. All the powders tested varied in the Mg silicate (dry basis) content indicated in Table 1. For tensile strength testing, each sample was subjected to compression using a single punch tabletting machine at a compression pressure of 80 MPa. Tablet weight and diameter (circular punch) were fixed at 400 mg and 12 mm, respectively. Tensile strength was measured using a hardness tester (Copley, Nottm Ltd., Therwil, Switzerland). The average crushing strength of 10 tablets was recorded for each sample. For disintegration time testing, the processed starch samples (by co-precipitation, by dry granulation, and by physical mixing) at the Mg silicate compositions shown in Table 1, were compressed to attain a tensile strength value of about 3.5 MPa. Compression was carried out using a single punch tabletting machine. Tablet weight and diameter (circular punch) were fixed at 400 mg and of 12 mm, respectively. The tablets were produced using a disintegration tester (Caleva, Dorset, UK) in accordance with USP 31 disintegration procedures for uncoated tablets.

2.11. Testing the effect of magnesium stearate on compact tensile strength

100.0 g of seven powder blends of starch-Mg silicate produced by co-precipitation or by dry granulation (for both techniques a Mg silicate content of 26.1% (w/w) was used; see Table 1) or starch 1500® or Lycatab® PGS physically mixed with Mg stearate at concentrations of 0.1, 0.2, 0.5, 1, 2, 3, 5% (w/w) were prepared. Mixing was performed manually in a 2 L Mini-blend v-blender (GlobePharma, New Brunswick, NJ, USA) operated at 30 rpm for 5 min. Each of the powder samples was subjected to compression using a single punch tabletting machine at a compression pressure of 80 MPa. Tablet weight was fixed at 400 mg. The circular punch size used was 12 mm.

2.12. Formulation with starch-Mg silicate

Five paracetamol preparations (500 g each) were prepared by physical mixing and direct compression. The five formulations had the following compositions.

Formula 1: 500 mg paracetamol: 150 mg starch-Mg silicate (coprecipitate);
Formula 2: 500 mg paracetamol: 150 mg starch-Mg silicate (compacted);
Formula 3: 500 mg paracetamol: 400 mg starch-Mg silicate (coprecipitate);
Formula 4: 500 mg paracetamol: 400 mg starch 1500® (partially pregelatinized starch);
Formula 5: 500 mg paracetamol: 400 mg Lycatab® PGS (fully pregelatinized starch).

The starch-Mg silicate powders resulting from the compacted and co-precipitated formulations had a Mg silicate content of 15.00% (w/w). All preparations were compressed using a single punch tabletting machine in which a 13-mm shallow concave punch was fitted. Compression was carried out and different forces were applied for different preparations so that the tensile strength of different tablets was maintained at around 3.0 MPa for the purpose of comparing drug release data. For drug dissolution studies, eight tablets were used according to USP specifications for the dissolution media and apparatus.

Table 2
Water flow rate (Q/t) and powder bed height (l) for the permeability experiments on the different types of starch (10 g) processed by physical mixing with 30% (w/w) of Mg silicate.

Starch type	Water flow rate (m^3/s)	Powder bed height (m)
MS	4.96E−10	0.028
CS	5.05E−09	0.030
PS	1.71E−08	0.037
RS	1.51E−08	0.043
Starch 1500®	4.31E−10	0.135
Lycatab® PGS	5.55E−10	0.119
MS + Mg silicate	1.40E−08	0.024
CS + Mg silicate	1.20E−08	0.025
PS + Mg silicate	2.80E−08	0.031
RS + Mg silicate	2.16E−08	0.037
Starch 1500® + Mg silicate	2.47E−09	0.088
Lycatab® PGS + Mg silicate	3.87E−09	0.092

3. Results and discussion

3.1. Water permeability of native and modified starch and the effect of Mg silicate addition

When starch granules from different plant species were subjected to water permeability tests, each species could be distinguished by its unique water flow characteristics under water saturated conditions and by the extent of swelling (expressed as the immersed powder bed height). The differences in water flow rate and degree of swelling resulted in variations in the calculated permeability (illustrated in Table 2 and Fig. 1, respectively). Maize starch and rice starch showed the lowest and highest permeability values, respectively. Such variations can be attributed to the difference in pore geometry of each type of starch upon swelling, as maize starch exhibited the lowest sediment bed expansion whilst rice starch had the highest (Table 2). This finding is in agreement with the work of Oyi et al. (2009) who reported a higher swelling capacity for rice starch compared to maize starch giving rise to more particle–particle interactions for maize starch and thereby less channeling capacity for water to penetrate. Furthermore, the permeability of potato starch was higher than both cassava and maize starches i.e. greatest swelling recorded was for potato starch. Gomand et al. (2010) refer to such swelling differences and attributed the behavior to the weak uniform bonds of the potato starch granules due to the presence of phosphate ester groups, resulting in relatively high repulsion between them.

When the permeability test experiments were carried out on the two types of commercial modified maize starch samples [partially pre-gelatinized starch (starch 1500®) and fully pre-gelatinized starch (Lycatab® PGS)] the resulting swelling (measured as the bed height elevation of the immersed saturated powder) was higher than all the other types of native starch (Table 2). However, the measured permeability values (0.23 and 0.27 μm/s for starch 1500® and Lycatab® PGS, respectively) were lower than for cassava, potato, and rice starch as indicated by the data in Fig. 1. Therefore, there must be factors other than the extent of swelling that affect powder permeability. More specifically, gelling of modified starches could hinder flow and penetration of water within their matrices (Herman et al., 1989a,b).

Since the primary objective of this research was to obtain a highly effective starch product in terms of disintegration and compaction properties of its compacts, the aim was directed towards increasing powder permeability. For this purpose, synthetic Mg silicate was initially added, by physical mixing, to the native and modified starches and the permeability of the resulting mixtures was examined. The data in Fig. 1 illustrate that Mg silicate, when present at a concentration of 30% (w/w), increases the permeability of the four native starch types (maize, cassava, potato, rice), and the two modified starches (starch 1500®, and Lycatab® PGS) by 2327, 197, 137, 122, 375, and 539%, respectively relative to all of the starch types without Mg silicate being added. The addition of Mg silicate reduces the measured bed height, in the permeability experiments, of all types of native and modified starch granules whilst increasing the outflow of water when compared to the granules without Mg silicate (Table 2). It is hypothesized that the Mg silicate affects the re-arrangement of the pore structure of the powder particle bed so as to reduce the particle–particle bonding thus allowing an additional/modified network of channels for water to penetrate.

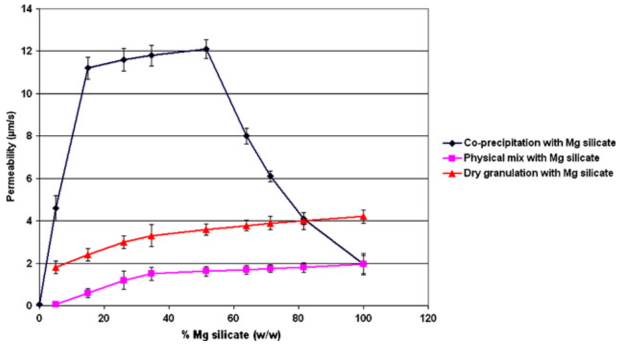

Fig. 2. Permeability data as a function of percentage of Mg silicate for samples of maize starch-Mg silicate prepared by different methods.

As the data in Fig. 1 indicate there is more than a 2000 fold increase in the permeability of maize starch when mixed with Mg silicate; therefore maize starch was chosen for processing with Mg silicate. The abundance and the low price of maize starch make it attractive for such uses. Two common industrial starch processing techniques, i.e. by co-precipitation of Mg silicate onto starch and by dry granulation, were chosen and subjected to analytical comparisons by conducting permeability experiments. Physical mixtures of maize starch with magnesium silicate were included for comparison purposes. Due to the high alkalinity of the treated starch product, the reaction of magnesium chloride with Na silicate and the resulting insoluble Mg silicate of moderate pH (8.0 ± 0.1) is an essential step when designing an acceptable grade of pharmaceutical powder.

3.2. Effect of processing technique and Mg silicate concentration on permeability of starch-Mg silicate

Generally, in swellable materials (such as starch) pore size, shape and interconnectivity can be adversely affected by contact

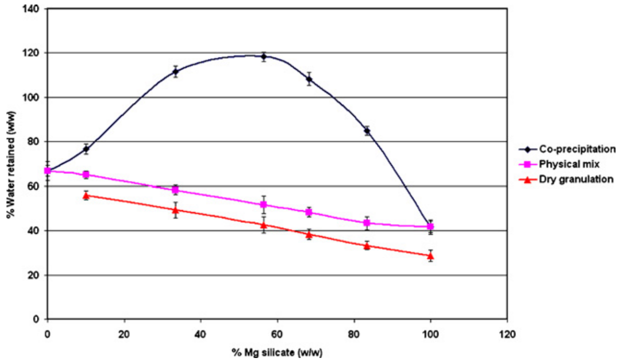

Fig. 3. Effect of different types of processing on the percentage water retention of maize starch as a function of percentage Mg silicate. All samples tested had a particle size range of 50–90 μm.

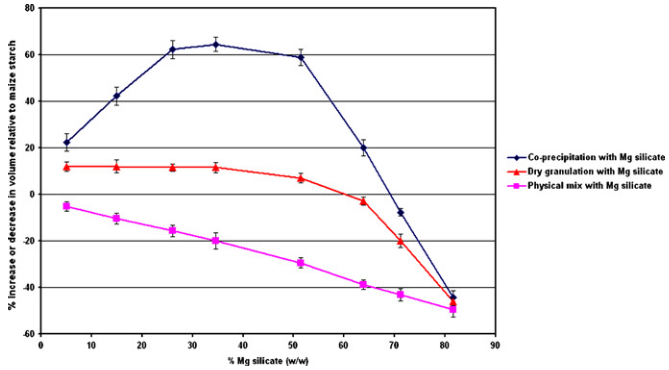

Fig. 4. Effect of different processing methods on the extent of swelling of maize. The extent of swelling is represented by the % increase or decrease in volume of the powder bed relative to unmodified native maize starch. All samples tested had a particle size range of 50–90 μm.

with aqueous solutions. Pore constriction and loss of connectivity will have an important impact in terms of reduction in permeability of the system (Oyi et al., 2009). The permeability of starch processed with Mg silicate by co-precipitation, dry granulation, and physical mixing is illustrated in Fig. 2 as a function of Mg silicate content. It is clear from the data presented in Fig. 2 that the permeability of starch-Mg silicate co-precipitate powder (particle size of 50–90 μm) is highest than that of the compacted and the physical mixture of starch with Mg silicate. As there is more Mg silicate within the starch-Mg silicate co precipitate, permeability increases to a maximum at a Mg silicate concentration of 51.4% (w/w). Above this concentration, permeability decreases to a minimum value representing that of Mg silicate alone (1.95 μm/s from the data in Fig. 2). Further process improvement was observed when maize starch and Mg silicate mixtures were dry granulated using roller compaction, compressed at 1.4 t (Fig. 2); the permeability level increases more than that of starch physically mixed with Mg silicate.

3.3. *Effect of processing technique and Mg silicate concentration on water retention of starch-Mg silicate*

The last data point (Fig. 2) in the permeability profile (100% Mg silicate) using the dry granulation technique, which represents the permeability of the compacted Mg silicate, is noteworthy. Compaction of Mg silicate increases permeability when compared to that of non-compacted Mg silicate due the decrease in water retention of Mg silicate when compacted. To verify the foregoing, water retention experiments using starch-Mg silicate via co-precipitation, physical mixing, and dry granulation (compaction) were conducted (Fig. 3). Dry granulation decreases the powder water retention of the physical mixture of starch-Mg silicate by almost 10%. This is due to the fact that when Mg silicate is compacted, it looses about 15% of its ability to retain water (Fig. 3). Hence, the increase in permeability of compacted starch-Mg silicate (Fig. 2) when compared to the physical mixture of starch with Mg silicate could be due to the decrease in the compacted powder's ability to retain water. The highest water retention and permeability values were obtained for starch-Mg silicate prepared by co-precipitation (Figs. 2 and 3). Theoretically, the powder with the smaller particle size can hold a large volume of water per volume of bulk material, but it does not release water very quickly (Horgan, 1996). The foregoing statement is valid for the physical mix and dry granulation techniques using starch with Mg silicate but it does not take into account water retention due to water uptake for particle swelling to take place. To clarify this issue the extent of swelling of the powders using different preparation techniques was tested (Fig. 4).

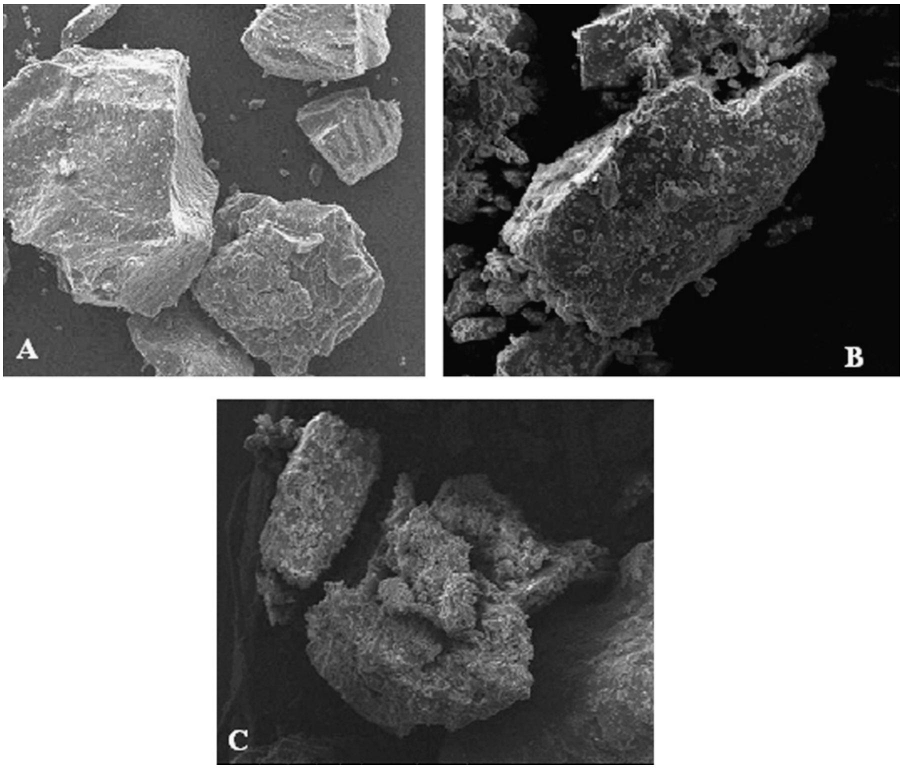

Fig. 5. Scanning electron microscopy data for maize starch (A), starch-Mg silicate (15.0% w/w Mg silicate) produced by co-precipitation (B) and by dry granulation (C) techniques. All pictures were magnified 200 times.

3.4. *Effect of processing technique and Mg silicate concentration on the swelling extent of starch-Mg silicate*

Starch-Mg silicate co-precipitate shows the highest extent of swelling when compared to the physical mixture and the dry granulation techniques (Fig. 4). In fact, the extent of swelling of starch-Mg silicate co-precipitate increases by e.g. 65% at a Mg silicate concentration of 34.6% from the initial increase encountered with native starch (taken as a reference). At the same point the physical mixture of starch-Mg silicate displays a 20% decrease in volume calculated on the same reference basis.

The data shown in Fig. 4 show a significant result regarding the extent of swelling of starch-Mg silicate when subjected to dry granulation using compaction. Although the extent of the powder swelling is in decreasing order as more Mg silicate is present within the starch granule structure (because concentration of Na silicate is increased to prepare Mg silicate), there is an increased degree of swelling compared to that of a physical mixture of starch with Mg silicate. Tester pointed out that when starch is subjected to high mechanical forces, using the ball mill technique, swelling and gel formation is facilitated due to the loss of the forces which prevent granules from swelling in water (Tester, 1997). In other words, consolidation of powders using compaction may optimize process parameters such as disintegration time which is directly related to the swelling ability of the particles.

3.5. *Analysis of compression data*

Analysis of the compression behavior of starch and Mg silicate, prepared by co-precipitation and dry granulation techniques, was investigated using Kawakita compression analysis. The Kawakita parameters for starch-Mg silicate co-precipitate, starch-Mg silicate by dry granulation of starch with Mg silicate at two concentrations of Mg silicate (20% and 80%), and Mg silicate are shown in Table 3. It is well documented that maize starch deforms plastically under pressure (Paronen and Juslin, 1983). In this respect, it is useful to determine the parameter $1/b$ which, as previously stated, provides an inverse measure of plastic deformation during compression. The lowest value of $1/b$ was obtained for starch-Mg silicate co-precipitate. Dry granulation resulted in higher $1/b$ values for the 20 and 80% starch compacts compared to that obtained for the co-precipitate. The lowest $1/b$ value for the dry granulation technique (and the closest to the $1/b$ value for the co-precipitation) was recorded for the 80% starch, i.e. 20% Mg silicate content. Generally, the lower the value of $1/b$ the higher the degree of plastic deformation occurring during compression (Adams and McKeown, 1996). Therefore, the plasticity after dry granulation of maize starch and Mg silicate is additive because of the high plasticity of the starch and moderately plasticity of the Mg silicate. The increase in plastic deformation will lead to more contact points for interparticulate bonding to produce stronger tablets (Nicklasson and Alderborn, 2000). This would favor starch-Mg silicate being produced by co-precipitation, which had the lowest $1/b$ value (high plasticity), when tablet tensile strength is important.

Data for the initial relative densities $(1-a)$ of the powders are shown in Table 3. Although all of the compressed powders had a unified particle size range of 50–90 μm, their $1-a$ values showed some variation between the powders (starch-Mg silicate) resulting from the two techniques (co-precipitation and dry granulation).These values provide a measure of the packed initial relative density of tablets upon application of low pressure (Podczeck and Sharma, 1996). Starch-Mg silicate co-precipitate showed an initial relative density of 0.55 g/mL which is close to its bulk density, measured as 0.58 g/mL. For starch-Mg silicate produced by dry granulation, the initial relative densities measured for the samples representing 20% and 80% starch were 0.32 and 0.31, respectively. These values are lower than the bulk densities of the 20% and 80% starch samples measured as 0.53 and 0.46, respectively. Therefore the powder produced by the co-precipitation technique undergoes less rearrangement and a higher finite ability for powder compression than that produced by dry granulation.

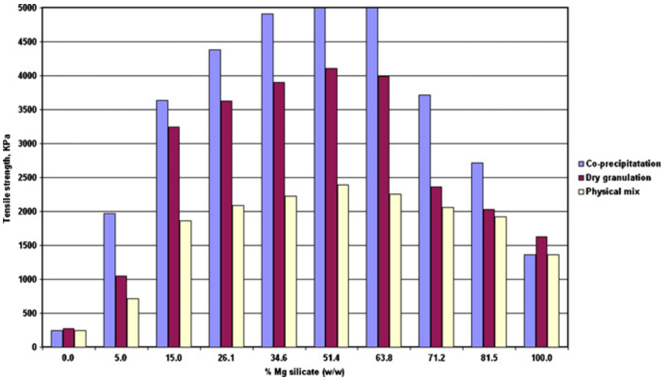

Fig. 6. Effect of processing technique on the tensile strength of maize starch tablets* as a function of % Mg silicate. *The tablets used were 400 mg in weight and 12 mm in diameter.

3.6. *Scanning election microscopy*

For plastically deforming materials, new clean surfaces are created under compression. Scanning electron microscopy (SEM) of maize starch reveals these clean surfaces (Fig. 5A). These smooth flat surfaces may be responsible for the low mechanical strength usually encountered with tablets made using maize starch, as there will be less number of contact points upon compression of the granules. Upon co-precipitation (15.0%, w/w Mg silicate), Mg silicate randomly covers these surfaces (Fig. 5B). Dry granulation of maize starch with Mg silicate produced highly deformed particles (Fig. 5C) unlike the highly regular compacts of starch observed in Fig. 5A.

3.7. *Tensile strengths of compacted powders*

The tensile strengths of tablets formulated using starch-Mg silicate and produced by different methods (all used as single components in tablet preparation) are shown in Fig. 6. Up to 64% (w/w) Mg silicate, the tablets produced by the two techniques show a large increase in tensile strength compared to their initial values (the 0% point) as the concentration of Mg silicate is increased. Tensile strength values were in the order: co-precipitation > dry granulation > physical mixture. Above a Mg silicate concentration of 64% (w/w), the tensile strengths of the compacts decreased due to the effect of the Mg silicate which has lower tensile strength (point 100% in the x-axis of Fig. 6). Analysis of the data in Fig. 6 reveals that compaction of Mg silicate alone slightly increases the compacts tensile strength.

3.8. *Disintegration time of compacted powders*

Using compacts from the two techniques, in addition to compacts from the physical mix, of a fixed tensile strength value around 3.5 MPa, disintegration time testing was carried out, the results of which are shown in Fig. 7. Although it was almost impossible to reach a tensile strength of 3.5 MPa for the physical mix tablets below Mg silicate concentrations of 26.1% (w/w), the two processes showed a decrease in disintegration time when compared to the physical mixture of starch and Mg silicate. Comparing the permeability data in Fig. 1, at 26.1% w/w Mg silicate, the permeability of starch-Mg silicate resulting from co precipitation and dry granulation is higher than that of the physical mixture of starch with

Table 3
Kawakita parameters for maize starch-Mg silicate co-precipitate [Mg silicate concentration of 15.0% (w/w)], Mg silicate, and two samples of maize starch-Mg silicate produced by dry granulation at starch concentrations of 20 and 80% (w/w). All samples tested had a particle size range of 50–90 μm.

Material	Slope (SD)	Intercept (SD)	*a*	*ab*	*b*	1/*b*	1 – *a*
Starch-Mg silicate co-precipitate	2.27 (±0.11)	19.68 (±2.1)	0.44	0.05	0.11	8.66	0.55
Mg Silicate	1.49 (±0.1)	32.15 (±1.0)	0.66	0.03	0.04	21.48	0.33
Starch-Mg silicate, dry granulation, 20% (w/w) starch	1.48 (±0.11)	23.13 (±2.2)	0.68	0.04	0.06	15.63	0.32
Starch-Mg silicate, dry granulation, 80% (w/w) starch	1.46 (±0.15)	18.94 (±2.0)	0.68	0.05	0.07	12.92	0.31

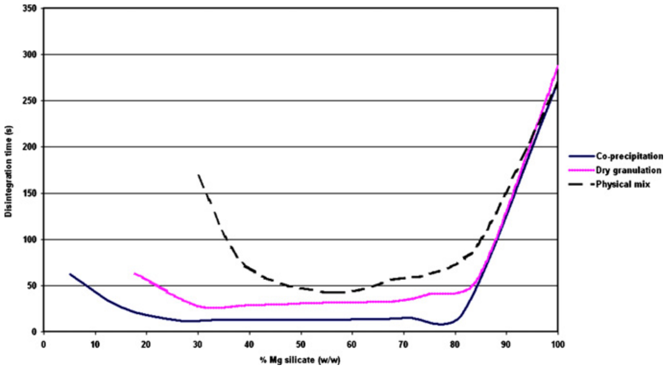

Fig. 7. Effect of processing technique on the disintegration time of maize starch as a function of % Mg silicate*. *Tablet weight and diameter (circular punch) were fixed at 400 mg and 12 mm, respectively.

Mg silicate. Hence the lower disintegration time attained for the physical mixture is a result of its higher permeability than the co precipitate and the dry granulated products.

3.9. *Effect of magnesium stearate addition on compacts tensile strength*

Starch-Mg silicate produced by co-precipitation or by dry granulation showed no deleterious effect on tablets tensile strength when Mg stearate is added up to a concentration of 5% (w/w) (Fig. 8). In contrast, starch 1500® and Lycatab® PGS showed a marked decrease in the tensile strength of the compacts which began at a magnesium stearate concentration of 0.1% (w/w) and ended in highly fragile compacts with no significant tensile strength at a Mg stearate concentration of 0.5% (w/w). Such a deleterious effect makes all native and commercial modified starch types less suitable for use in direct compression unlike starch-Mg silicate which demonstrated its suitability of use. The functionality of synthetic Mg silicate as an adsorbent to fatty acids is suggested to significantly minimize the deleterious role of Mg stearate on tablet compaction (Rashid et al., 2010; Ciesielczyk et al., 2007). This is due to the presence of the silanol groups (≡Si–OH) as the most active groups on the surface; they normally provide the site for physical adsorption of organic particles (Iler, 1979), more specifically those which carry a positive electrostatic charge e.g. Mg stearate (Vigil et al., 1994).

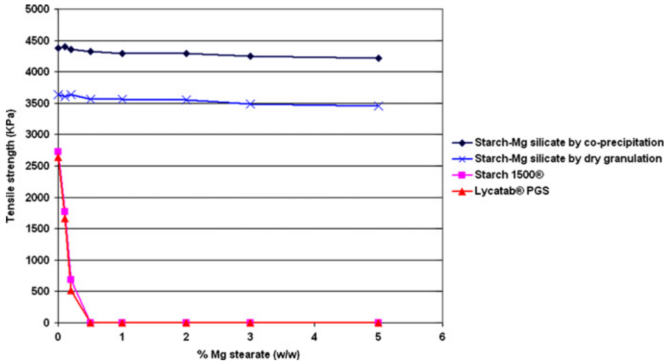

Fig. 8. Effect of magnesium stearate concentration on tablet crushing strength of starch-Mg silicate produced by co-precipitation or by dry granulation or starch 1500® or Lycatab® PGS physically mixed with magnesium stearate at concentrations of 0.1, 0.2, 0.5, 1, 2, 3, 5% (w/w). Tablets, 12 mm in diameter and weighing 400 mg each were used. Compression pressure was set at 80 MPa.

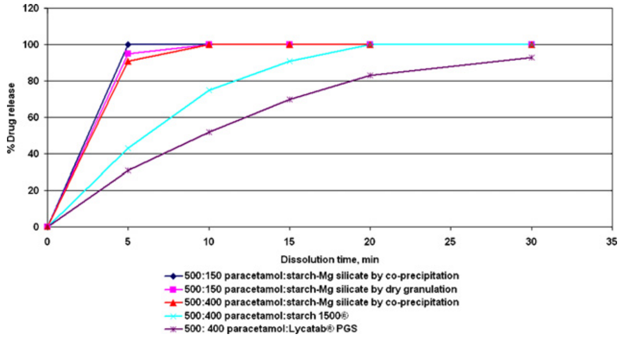

Fig. 9. Dissolution profile of five paracetamol formulas using starch (maize)-Mg silicate produced by co-precipitation and dry granulation techniques using commercially modified starches, starch 1500® and Lycatab® PGS*. *The starch-Mg silicate powder resulting from the two methods had a Mg silicate content of 15.0% (w/w). Tablets were 13-mm shallow and concave. Tablet tensile strength was fixed at about 3.0 MPa. Tablet weight was 650 mg for the formulas containing 23.1% (w/w) processed starch and 900 mg for formulas containing 44.4% (w/w) of either processed starch or commercially modified starch.

3.10. *Dissolution of paracetamol compacts formulated by direct compression*

The poor flow and compaction properties of paracetamol as an active ingredient in drug formulation would place paracetamol a good model for formulation with starch-Mg silicate. Paracetamol tablet preparations with starch-Mg silicate produced by co-precipitation and by dry granulation (both at a percentage Mg silicate of 15.0% (w/w)), as well as preparations with starch 1500® and Lycatab® PGS, all prepared by direct compression resulted in the dissolution profiles shown in Fig. 9. It is clear from the data presented in Fig. 9 that almost full drug release was established between 5 and 10 min of dissolution time for both techniques carried out on starch-Mg silicate at the starch-Mg silicate content of 23.1% (w/w) within the tablets. At the starch-Mg silicate content of 44.4% (w/w), full drug release was still maintained within 5–10 min of dissolution time. The later result was not achieved when using starch 1500® and Lycatab® PGS, both at the concentration of 44.4% (w/w) in the formula. Full drug release was recorded at the 20 min of dissolution time for starch 1500® and estimated to be greater than 30 min for Lycatab® PGS. It is clear that the low permeability of the commercially available modified starches may impart some degree of retardation of drug release which could be accelerated by the incorporation of Mg silicate.

4. Conclusions

The experiments reported herein show that the permeability of different types of starches differs. In addition, permeability testing has proved to be a useful technique for highlighting the important role of Mg silicate as a permeability enhancing agent due to its inherent anti-adhering characteristics. Starch processed with Mg silicate, using co-precipitation or dry granulation, can be used as a multifunctional excipient with the required binding and disintegration properties. Powder compression using Kawakita analysis confirmed the higher plasticity and lower degree of rearrangement of starch-Mg silicate resulting from co-precipitation compared to dry granulation. In addition, co-precipitation imparts high surface micro-irregularities as evidenced by SEM analysis. Formulation of a high strength model drug with starch-Mg silicate illustrated the efficiency of the highly permeable starch-Mg silicate in attaining quick drug release when compared to formulations with commercially available modified starch.

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