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Preformulation Studies and Compaction Properties of a New Starch-Based Pharmaceutical Aid

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ABSTRACT

Pregelatinized starches (PGS), as thermal modifications of starches, have improved flow and disintegrant properties in tablet formulations. The drawback of pregelatinized starch preparations is that it takes longer time to dry, even in an air oven, hence requiring enormous energy consumption. Acetone precipitation of the gelatinized starch was found to preclude this limitation. Two methods were used - cold and hot precipitations and the physical, compaction and disintegration characteristics studied. The results revealed that the acetone treated pregelatinized starch (APGS $_{(cold), (hot)}$) did not only retain the good powder properties of PGS but improved on them. The DSC and FTIR results for APGS were similar to that of PGS, indicating that the observed improved properties were not due to chemical changes in the starch granules. The SEM pictures show no observable morphological differences. The compaction characteristics showed that the mean yield pressure values calculated from the linear region of the Heckel plots as well as area under the Heckel curves values indicated APGS $_{(cold), (hot)}$ to be the more ductile materials. The tensile strengths of APGS $_{(cold), (hot)}$ compacts increased linearly with increasing applied pressures and indicate that the APGS $_{(cold), (hot)}$ formed stronger compacts. The compacts of the APGS $_{(cold), (hot)}$ were intact in water after 4 h and swelled considerably, while the PGS compacts disintegrated within 10 min. Consequently, it was concluded that the APGS $_{(cold), (hot)}$ are superior dry binders and potential controlled release matrixing agents to PGS.

Keywords: Modified pregelatinized starch; **Preformulation**; Compaction; Disintegration properties; Pharmaceutical aid

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INTRODUCTION

Starch is widely used in the production of pharmaceuticals because of its relative inertness, wide availability, low cost and high functionality. These uses are mainly due to its adhesive, thickening, gelling, swelling and film forming properties [1]. Pharmaceutical grade starch can be obtained from various sources depending on the ease of extraction, abundance of the material in any particular location as well as cost. Native starches are however limited in their use due to their large molecular size, insolubility in water, instability of the viscous solution and susceptibility to microorganisms [2]. Chemical modifications like oxidation, acid-treatment, etherification, esterification, grafting and preparation of poly (vinyl)-starch composites have been advocated to overcome such problems [3].

Pregelatinized starches (PGS), as thermal modification of starches, have been reported in literature [4] to improve flow characteristics of starches and disintegrant properties of tablets. Herman and Remon [5] have also reported that these starches are suitable as matrices for controlled oral delivery of drugs. The drawback of pregelatinized starch preparations is that they take longer time to dry, even in an air oven, hence requiring enormous energy consumption. This paper reports on a novel modification of the process of pregelatinization which overcomes this observed drawback. The physical, compaction and disintegration properties of these novel modified pregelatinized starches were compared with that of conventionally prepared pregelatinized starch.

MATERIALS AND METHODS

Materials

These include maize starch B.P, sodium hydroxide (BDH Chemicals Ltd., Poole, UK), acetone (M & B, England) and distilled water. All other chemicals used were of analytical or reagent grade.

Methods

Preparation of pregelatinized starch (PGS)

A 300 g quantity of maize starch was suspended in 2.0 L of distilled water at room temperature. The suspension was heated to 90˚C in a water bath with occasional stirring until the starch was gelatinized. The paste obtained was thinly spread to a thickness of about 5 mm on stainless steel trays and dried in an air oven at 60˚C for 48h. The flakes were powdered using a blender (Moulinex®, France) and sieved. Powder fraction of size ≤ 1.0 mm was used for this investigation.

Preparation of acetone treated pregelatinized starch

The same procedure as above was used, except that the resulting mucilage was then precipitated using 3.0 L of acetone. Precipitation was achieved at both 90˚C and room temperature; and since the boiling point of acetone is 56˚C there was accompanying boiling during the hot precipitation. The precipitated products which are rubbery masses were cut into small lumps and then dried in a fluidized bed dryer for 1 h at an inlet temperature of 60˚C. The resultant dried materials, coded APGS $_{(cold)}$ and APGS $_{(hot)}$ respectively, were size reduced using a blender (Moulinex®, France) and sieved. Powder fraction of size ≤ 1.0 mm was used for this investigation.

Physical characterization

Particle size analysis

This was done by sieve size analysis using a sieve-shaker, (Retak 3D, Retsch GmbH and Co KG, Haan, Germany). Test sieves ranging from 1000- to 150- µm were arranged in descending order. A 20 g quantity of the powder was placed on the top sieve and the set-up was shaken at an amplitude of 1.50 mm/g for 5 min. The weight of material retained on each sieve was determined. The average diameter was computed as reported by Ansel et al [6] using the equation:

Average diameter = [∑ (% retained) x (mean aperture)]/100 ….1

True Density

The true density (D_t), of powder sample was determined by the liquid displacement method using xylene as the immersion fluid [7] and computed according to the following equation:

$$D_t = \{w/[(a + w)-b]\} \times SG \ldots 2$$

Where *w* is the weight of powder, SG is specific gravity of solvent, *a* is weight of bottle + solvent and *b* is weight of bottle + solvent + powder.

Scanning electron microscopy

Scanning electron microscopy (gold coating, Edwards Sputter Coater, UK) was performed using a Joel 6310 (Joel Instrument, Tokyo, Japan) system running at 10 KeV.

Angle of Repose

The static angle of repose, *a,* was measured according to the fixed funnel and free standing cone method [8], and the tangent of the angle of repose calculated using the equation:

Tan *a* = 2h/D….3

Where h is the height of the heap of powder and D is the diameter of the base of the heap of powder.

Bulk and Tap Density

A 10 g quantity each of the powder samples was, placed into a 50 ml clean, dry measuring cylinder and the volume, V_o, occupied by each of the samples without tapping was determined. After 500 taps using Stampfvolumeter (Model STAV 2003 JEF, Germany), the occupied volume, V_{500}, was determined. The bulk and tap densities were calculated as the ratio of weight to volume (V_0 and V_{500} respectively) [7].

Additionally, to measure the propensity of the samples to be compressed the *Hausner Index* was calculated as the ratio of tap density to bulk density of the samples and *Compressibility Index* as:

Compressibility (%) = {(Tapped density – bulk density)/Tapped density} x 100 %....4.

Powder Porosity

This was derived from the values of true and bulk densities when fitted into the Eqn 5 [7]:

$$e = \{1 - B_b/D_t\} \times 100 ....5$$

Where B_b is the bulk density, D_t is the true density and *e* is the porosity.

Hydration Capacity

The method of Kornblum and Stoopak [9] was used. A 1.0 g quantity of each of the samples was placed in each of four 15 ml plastic centrifuge tubes and 10 ml distilled water was added and then stoppered. The contents were mixed on a vortex mixer (Vortex-Gennie Scientific Industry, USA) for 2 min. The mixture was allowed to stand for 10 min and immediately centrifuged at 1000 rpm for 10 min. on a bench centrifuge (Gallenkamp, England). The supernatant was carefully decanted and the sediment weighed. The hydration capacity was taken as the ratio of the weight of the sediment to the dry sample weight.

Swelling capacity

This was measured at the same time as the hydration capacity using the method of Okhamafe et al [10] and computed according to the following equation:

$$S = \{(V_2 - V_1) / V_1\} \times 100 ....6$$

Where S is the % swelling capacity, V_2 is the volume of the hydrated or swollen material and V_1 is the tapped volume of the material prior to hydration.

Moisture Sorption profiles

Two grams of the sample materials were accurately weighed and evenly distributed over the surface of a 70 mm tarred *Petri* dish. The samples were then placed in a large desiccator containing distilled water in its reservoir (RH = 100%) at room temperature and the weight gained by the exposed samples over a seven-day period was recorded and the amount of water sorbed was calculated from the weight difference [1].

Loss on drying

Five grams of powder sample was transferred, each, into a *Petri* dish and then dried in an oven at 105°C until a constant weight was obtained. The % moisture content was then determined as the ratio of weight of moisture loss to weight of sample expressed as percentage [10].

Differential Scanning Calorimetry (DSC)

DSC scans of the powdered samples were recorded using the DSC 204 F1 (Netzsch Geratebau, GmbH, Selb, Germany), a heat-influx DSC equipped with Netzsch Thermokinetic Analysis Software. The thermal traces were obtained by heating from 26°C to 500°C at a heating rate of 10°C under inert nitrogen dynamic atmosphere (70 ml/ min) in close aluminum pan with lid pierced and an empty pan was used as the reference.

Fourier-transform infrared spectra

The surface of each sample was characterized using Perkin-Elmer Spectrum 100 Fourier transform infrared (FTIR) Spectrophotometer. Each sample was scanned 28 times at a resolution of 4 cm^{-1} between 4000 and 650 cm $^{-1}$.

Compression and Compaction studies

Preparation and analysis of compacts

Compacts of weights 400mg of each of the starch sample materials were made using a single punch power-driven tablet press (Shanghai Tianxiang and Chentai Pharmaceutical Machinery Co. Ltd., China) at compression pressures from 7 to 14 units, corresponding to the compression pressures of 17.5 to 35 KN, respectively. Twenty were made at each compression level. Before compression, the die (10.5 mm diameter) and the flat- faced punches were lubricated with a 2% w/v dispersion of magnesium stearate in ethanol-ether(1:1).The compacts were stored in an air-tight container for 24hours (to allow for elastic recovery and hardening and prevent falsely low yield values) before evaluations. The dimensions {thickness (t) and

diameter (D)} and weight uniformity of ten compacts were determined. The compact diametral crushing strength (C_s) was determined using an Erweka hardness tester (model MT, Germany). The relative density D was calculated as the ratio of density of the compact, D_t, to the particle density, D_p, of the starch samples. The data obtained using this 'ejected tablet method' were used to obtain the Heckel plots and linear regression analysis was carried out over a compression range of 22.5 to 30.0 KN and parameters from Heckel plots calculated. The area under the Heckel curve (AUHC) was calculated by the trapezoidal method, and used to express the extent of volume reduction (ie, compressibility) that the material had undergone during the entire compression pressure range.

The compaction characteristics of the powders were studied using Heckel equation (Equation 7)[11, 12]:

$$\ln 1/1\text{-}D \quad = KP + A \qquad\qquad ....(7)$$

Where D is the density of the compact relative to the particle density of the material being compacted, P is the applied pressure, K (the slope of the straight line portion) is the reciprocal of the yield pressure, Py, of the material. The yield pressure is inversely related to the ability of the material to deform plastically under pressure and A is a function of the original compact volume. From the intercept A, the relative density D_a, can be calculated using the equation 8:

$$D_a = 1\text{-}e^{-A} \qquad\qquad ....(8)$$

The relative density D_0, of the powder at the point when the applied pressure equals zero ($D_0 =$ loose density/particle density) is used to describe the initial rearrangement phase of densification as a result of die filling and high value indicating very dense packing.

The relative density D_b, describes the phase of arrangement during the initial stages of compression. The extent of this depends on the theoretical point of densification at which particle deformation begins. D_b is obtained from the difference between D_a and D_0.

$$D_b = D_a - D_0 \qquad\qquad .....(9)$$

The tensile strength (Ts) was calculated from:

$$Ts = 2C_s/\pi Dt \qquad\qquad ...... (10)$$

in accordance with Fell and Newton's expression [13]. The tensile strength values were then plotted against the respective compression pressures. The area under the tensile strength versus compression pressure curves (AUTSC) was calculated by the trapezoidal method. This is a measure of the compactibility of the material (ie, strength of the tablets) [14].

Disintegration time

The disintegration time of the compacts was determined in distilled water at 37°C using

a BP disintegration test unit (Manesty Machines, Poole, UK). The disintegration times reported are the mean of 6 determinations.

RESULTS AND DISCUSSIONS

Fig. 1 shows that the comparative cumulative frequency distribution (undersize) of the PGS and APGS (cold), (hot) powder is similar. The calculated mean particle diameters are 312, 416 and 680 µm for PGS, APGS (hot) and APGS (cold), respectively.

The results of the other powder properties investigated are shown in Tab.1.The true density for PGS was slightly higher than that of the APGS (cold), (hot). Since powders normally flow under the influence of gravity and dense substances are generally less cohesive than lighter ones [15]; it would be expected that PGS will flow better than APGS (cold), (hot). This inference was not supported by the flow properties.

Fig.2 shows SEM pictures of the treated and conventional pregelatinized starches in comparison to the native corn starch BP. The pregelatinized starches have lost their original starch grain shape and among them there is no much observable morphologically differences.

The flow properties of powders are essential in determining the suitability of a material as a direct compression excipient. The angle of repose, Hausner index and Carr's percent compressibility are considered as indirect measurements of powder flowability [16]. The angle of repose for the APGS (cold), (hot) and PGS were small (Tab. 1). The Hausner index is indicative of inter-particle friction, while the Carr's index shows the aptitude of a material to diminish in volume. As the values of these indices increase, the flow of the powder decreases. In general however, a Hausner ratio less than 1.25 indicates free flow and Carr's compressibility index below 16% indicate good flowability while values in the range of 28 - 35% indicate poor flow [17]. Thus, the flow indices as assessed by indirect methods showed that the powders were free flowing. Additionally, the flow rate which is a direct method of assessing flow properties supports this assertion. It is explained that the free flowing of the powders in spite of their relatively high moisture content is due to their granular nature. On the basis of the flow indices the order of flow is APGS (cold) = APGS (hot) > PGS.

Swelling which is generally accepted as an indication of tablet disintegration ability [18] can be assessed by the determination of hydration capacity, swelling capacity and moisture sorption profile. The hydration capacity (Hc) values (Tab. 1) indicates that the APGS (cold), (hot) are capable of absorbing and retaining more water than PGS. The swelling capacity which reflects the increase in volume of samples following water absorption, followed the same trend as the hydration capacity index. This large hydration and swelling of APGS (cold), (hot) relative to PGS could indicate that acetone treatment resulted in more "destructurisation" of starch granules in the APGS (cold), (hot) resulting in increased rate and extent of water penetration. The results suggest that APGS (cold), (hot) may be exhibit different disintegration and controlled release

properties in comparison to PGS when incorporated in tablet formulations as either a disintegrants or as a matrixing agent.

Fig. 3 shows the moisture sorption profile of the APGS $_{(cold), (hot)}$ and PGS. This property is a measure of moisture sensitivity of material and its knowledge is necessary where controlled powder flow or compaction is critical. Moisture modifies the flow and mechanical properties of many powders including starches [19]. The result shows that PGS has high rate of water sorption compared to the APGS $_{(cold), (hot)}$. This indicates that it is relatively more sensitive to atmospheric moisture and should therefore be stored in air- tight containers. In addition, the higher the rate of moisture sorption the higher will be the deteriorating effect on incorporated drugs that undergo hydrolytic decomposition. Consequently, the APGS $_{(cold), (hot)}$ which have low moisture sorption profile would be preferred when formulations involving these categories of drugs are considered.

In most of the papers in literature, the DSC thermograms of starch materials are about the study of sol-gel reversible transtition in aqueous solution [19, 20]. The analysis of this phenomenon is made at the temperature range between 10 and 135˚C. The evaluation made in this study was intended to characterize the acetone treated pregelatinized starch in comparison to the untreated pregelatinized and, for that reason, the DSC thermograms were analyzed in the range from 26 to 350˚C. The thermogram that is presented in Fig. 4 shows an endotherm of dehydration, in which the peaks are centered between 58 and 61˚C. This endotherm present on this thermogram may be due to interaction of water and the hydroxyl groups of the starch material. These endotherms seem to have correlation with the determined moisture contents; it is broadest for the PGS whose moisture content is 12%, followed by APGS$_{(hot)}$ (m.c = 10%) and then the APGS$_{(cold)}$ having a moisture content of 9.2%. The second endotherms which are due to the melting of the crystalline regions and to the degradation of the pregelatinized starches, have peaks between 320 and 321˚C and almost similar enthalpy change between 234 and 241 J/g. This can be ascribed to similarity in the 'starch' intramolecular bonds and degree of crystallinity as well as similar degree of pregelatinization. It could be inferred that precipitation with acetone has no effect on these properties. It is observed that while the thermal analysis of aqueous starch system has detectable glass transition as one of the phase transitions, the thermograms of the pregelatinized starches did not show clear glass transition temperature. Oudhuis [21] has reported that sub-Tg endotherm (i.e. endotherm due to water desorption), sometimes, is superimposed on the glass transition. The similarity of the thermograms, in general, indicate that observed powder properties change are due to physical rather than chemical change.

It has been shown previously that FT-IR is a powerful technique for elucidation of structural changes of carbohydrate samples, with the ability to discovering differences not seen by other physicochemical analyses [22]. In the FTIR spectra (Fig.5) of the pregelatinized starch samples an intense band at 1638 is present, assigned to deformational vibrations of water molecules absorbed by the starch samples. The FTIR spectra of all the samples exhibited the following absorption bands: 2928 cm^{-1} (C-H symmetric stretching), 1357 cm^{-1} (O-C-O symmetric

bending) and the three bands between 1200 – 1000 cm^{-1} (C-C and C-O stretching). The corresponding spectra of the APGS$_{(hot), (cold)}$ (spectra not shown) were very similar to those obtained for the PGS. Any substantial chemical change within the starch structure should have resulted in shifts of bands occurring at 2928 and 1200 – 1000 cm^{-1} where hydrogen bonding in samples is apparent. However, there was no evidence of spectral difference in these regions was found with the APGS$_{(hot), (cold)}$. The bands at 927 and 760 cm^{-1} result from the pyranose ring vibrations. In general, the FTIR spectra, like the DSC results, indicate that the acetone treatment does not cause changes in the chemical bonding within the structure.

The Heckel analysis is routinely performed to study the effect of applied pressure on the relative density of powder during compaction and to determine the deformation mechanism of particles forming compacts [23, 24]. The Heckel plots for the APGS$_{(hot), (cold)}$ and PGS are shown in Fig. 6 and Tab. 2 shows the Heckel constants derived from the plots. The plots for the APGS$_{(hot), (cold)}$ were similar, showing discernible initial curves region (17.5-22.5 KN)- an indication of fragmentation tendencies of the materials [24]; as well as linearity over the compression range of 22.5-30.0 KN, indicating that the mechanism of consolidation of the material were similar, predominantly plastic deformation. In contrast, the Heckel plot for PGS, in general, is non linear, indicating fragmentation propensity [24].

The slope of the linear portion, K, can be correlated to the crushing strength of compacts; larger values of K usually indicate harder compacts [25]. The K values for the APGS$_{(hot), (cold)}$ are comparable. Consequently, the APGS$_{(hot), (cold)}$ with high K values would be expected to form harder compacts while the PGS forming weak compacts. The tensile strength determination (Fig. 7) is supportive of this inference.

The mean yield pressure, P$_y$, is inversely related to the ability of the material to deform plastically under pressure [12, 26]. While the P$_y$ values for the APGS$_{(hot), (cold)}$ (Tab. 2) are comparable their values are obviously lower compared to that of PGS. This however could not be explained on the basis of calculated mean particle diameters (of 312, 416 and 680 µm for PGS, APGS $_{(hot)}$ and APGS $_{(cold)}$, respectively) and hence contact areas. Although the DSC results showed similarity of intramolecular bonds and degree of crystallinity, the observed differences in P$_y$ values of the APGS$_{(hot), (cold)}$ and PGS could indicate that APGS$_{(hot), (cold)}$ underwent plastic deformation more easily and rapidly than the PGS under pressure. It seems that the acetone treatment during the preparation of APGS$_{(hot), (cold)}$ resulted in more destructurisation and subsequent weakening of the starch granules resulting in more particle- particle interaction, possibly from more new bond formation, when pressure was applied.

Using area under the Heckel curve (AUHC) to estimate the extent of compressibility [27], the slightly greater compressibility of APGS$_{(hot)}$ compared to APGS$_{(cold)}$ became more evident. However, this conclusion could not be made on the basis of R^2 values. Kumar et al [27] had earlier reported that a coefficient of determination (R^2) value close to unity is indicative of plastic deformation, whereas decreasing values suggest fragmentation propensity.

The relationship between the tensile strength of the APGS $_{(cold), (hot)}$ and PGS compacts and the respective compression pressure is shown in Fig. 7. While it was possible to produce strong APGS $_{(cold), (hot)}$ compacts at compression pressures as low as 17.5 KN, PGS could not form compacts at 25.0 KN. This indicates a high functionality for the APGS's. The AUTSC values (Tab. 2), however, clearly show that the APGS $_{(cold),}$ formed the strongest compacts, followed by APGS$_{(hot)}$ and then PGS.

Tab. 3 shows the relationship between the compressional pressures and disintegration times of the PGS product. Interestingly, the compacts of APGS $_{(cold), (hot)}$ were intact in water for more than 4 h and swelled considerably. These results suggest that the APGS $_{(cold), (hot)}$ are superior binder as well as better matrixing agents for controlled release of medicaments than PGS.

CONCLUSION

Acetone precipitation of the gelatinized starch was found to preclude the observed drawback of longer drying time of pregelatinized starch preparations. The acetone treatment affects its physical, compaction and disintegration properties. Powder flow properties and the hydration and swelling capacities and moisture sorption profile, are most affected positively. The extent of the effect observed is largely not dependent on the method of precipitation. The DSC and FTIR results were similar for the materials, indicating that the observed improved properties could have resulted from physical rather than chemical changes in the starch granules. While the compaction characteristics showed APGS $_{(cold), (hot)}$ to be the more ductile and compactible materials than the PGS, there was no significant difference in compaction characteristic between the APGS $_{(cold), (hot)}$. The disintegration properties showed PGS to disintegrate within 10 min while the APGS $_{(cold), (hot)}$ compacts were intact in water even after 4 h and swelled considerably. Consequently, it was concluded that APGS $_{(cold), (hot)}$ would be superior dry binders and potential controlled release matrixing agents to PGS.

Tab. 1: Powder properties of PGS and APGS (cold), (hot)

Parameters	PGS	APGS (Hot)	APGS (Cold)
True density (g/ml)	1.49(0.07)	1.36 (0.12)	1.42(0.06)
Bulk density (g/ml)	0.67 (0.06)	0.71 (0.55)	0.67 (0.04)
Tapped density (g/ml)	0.91 (0.04)	0.83 (0.06)	0.79 (0.12)
Porosity (%)	55	48	53
Flow properties:			
(a) Angle of repose	30.4(2.24)	29.1 (1.62)	26.7 (0.56)
(b) Hausner index	1.36	1.18	1.17
(c) Compressibility index (%)	24.4	14.5	15.0
(d) Flow rate (g/sec)	3.2	3.61	5.02
Hydration capacity	3.88(0.04)	8.91 (0.66)	9.9 (0.52)
Swelling capacity (%)	191.7 (2.70)	434 (5.14)	579 (6.03)
Loss on drying (%)	12.0 (2.0)	10.0 (1.06)	9.2 (1.84)

Values in parenthesis represent standard deviations of four determinations.

Tab. 2: Parameters derived from Heckel plots for APGS (cold), (hot) and PGS excipients

Starch products	R^2	AUHC [KN]	K	A	P_y [KN]	AUTSC [M N/m^2.KN]
APGS (hot)	0.9546	21.66	0.1283	2.1203	7.7942	1.573
APGS (cold)	0.9933	20.76	0.1162	1.8764	8.6059	2.358
PGS*	1.0	8.21	0.0715	0.9690	13.9860	0.040

* Linearity was taken between two points at compression pressures of 27.5-30 KN

Tab. 3: Compressional pressures and disintegration times for PGS

Compression pressures [KN]	Disintegration times [sec] PGS
17.5	*
20.0	*
22.5	*
25.0	*
27.5	11
30.0	231
32.5	300
35.0	540

* No compact was formed at these compressional pressures.
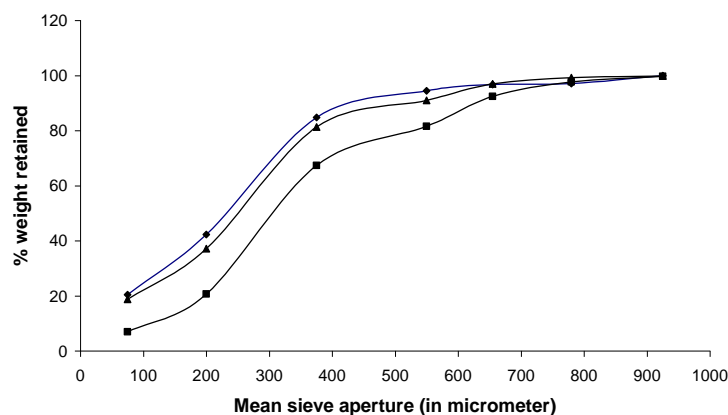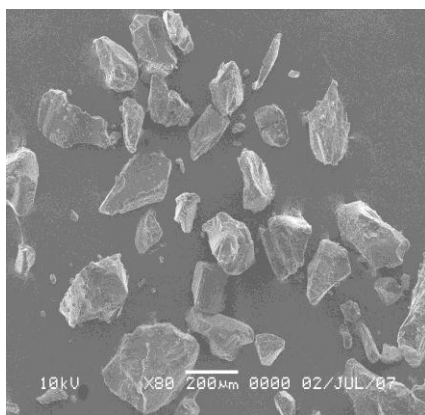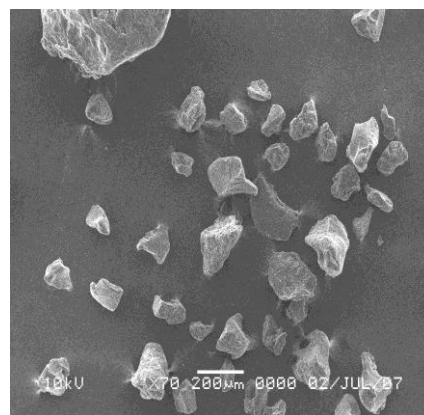

Fig. 1: Particle size distribution of PGS [▲] and APGS's [♦]cold, [■]hot.

(A)

(B)

(C)

(D)
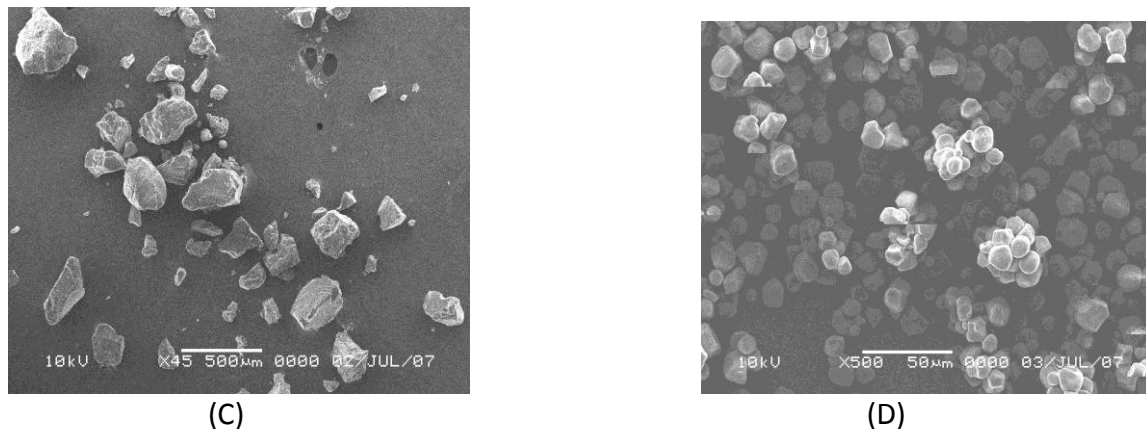
Fig. 2. Scanning electron micrographs of **(A)** PGS **(B)** APGS$_{hot}$ **(C)** APGS$_{cold}$ **(D)** Corn Starch
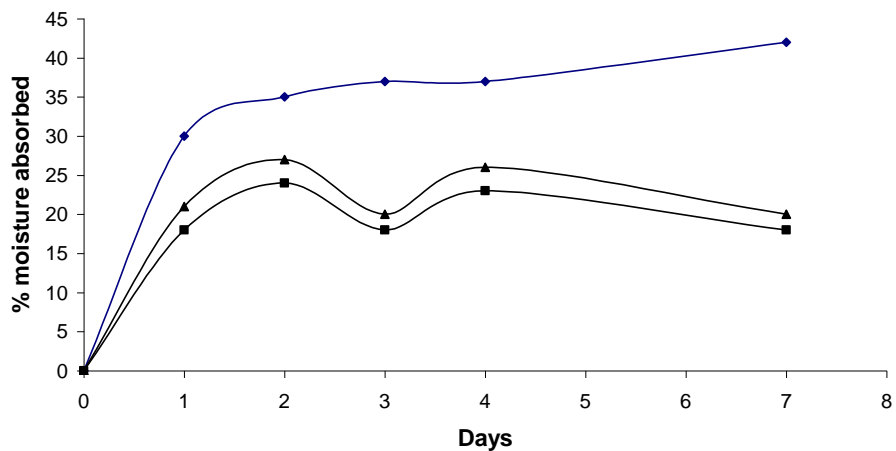
Fig. 3: Moisture Sorption Profile of PGS (♦) and APGS's (▲[cold], ■[hot])
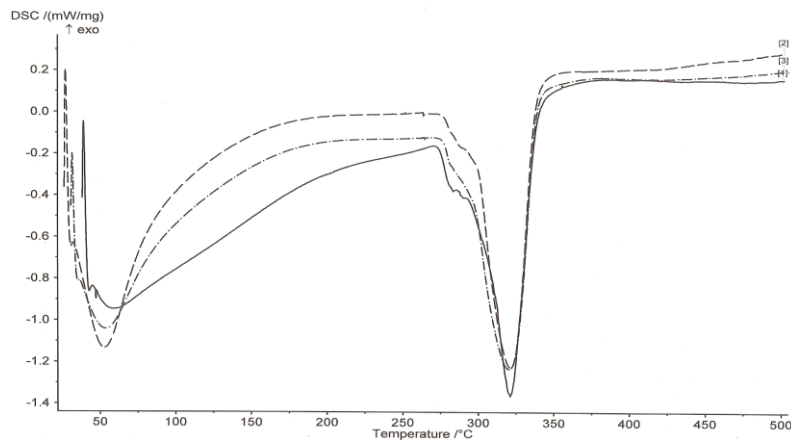
Fig. 4. DSC Thermograms of the Pregelatinized Starches. PGS [1], APGS_{cold} [2], APGS_{hot} [3],
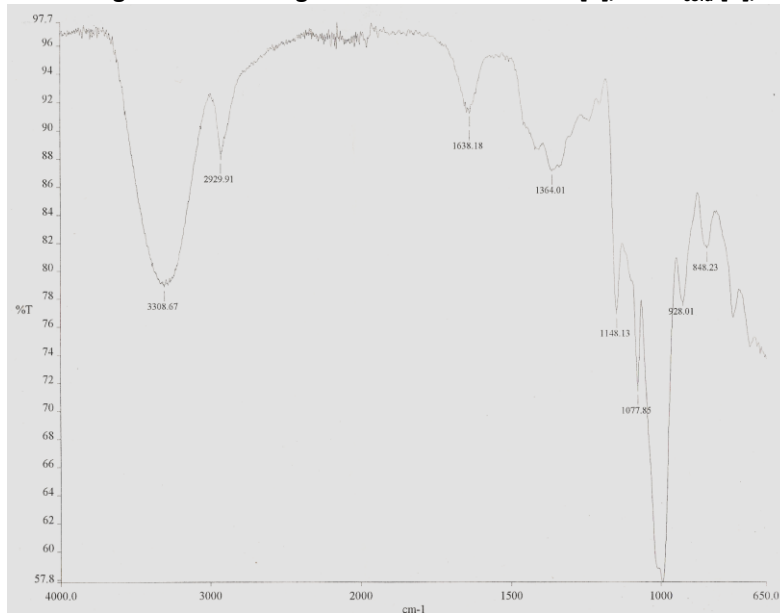

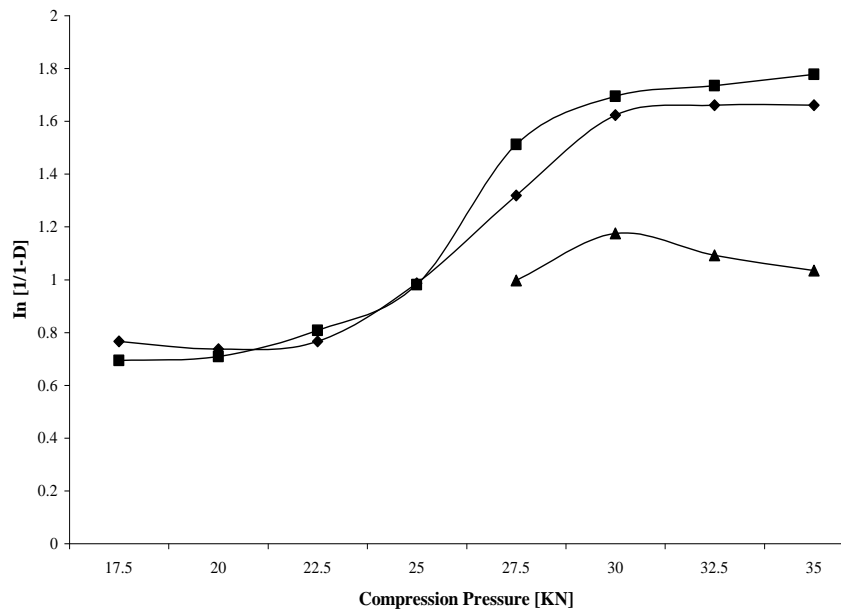**Fig. 5. Infrared Spectroscopy (FTIR) spectra of the Pregelatinized Starch (PGS)**

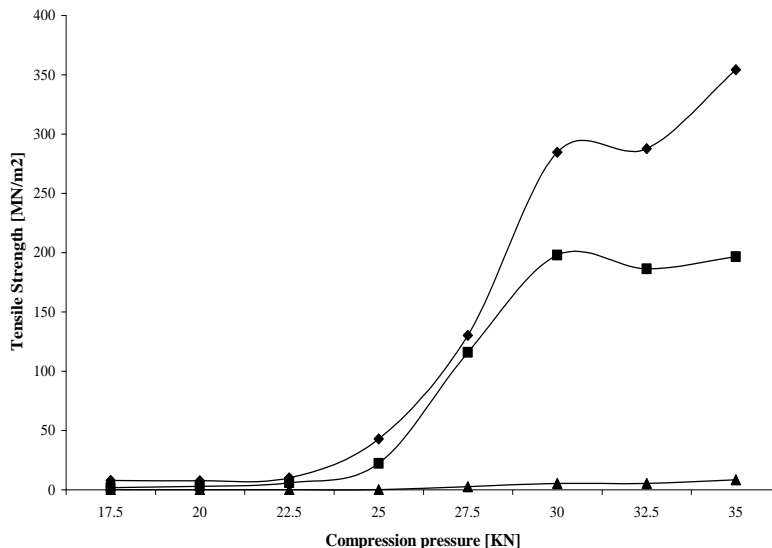**Fig. 6.** Heckel plots for [■]APGS(hot), [♦]APGS(cold) and [▲]PGS

Fig. 7. The Relationship between tensile strength and the applied pressures for
[■]APGS(hot), [♦]APGS(cold) and [▲]PGS

LEGENGS

Figures 1, 2, 6, 7
[■]   represents APGS(hot)
[♦]   represents APGS(cold)
[▲]   represents PGS

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