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EFFECT OF HUMIDITY ON THE DISINTEGRANT PROPERTY OF α-CELLULOSE

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Abstract: A study has been carried out to investigate the effect of humidity on the disintegrant property of α-cellulose in paracetamol tablets. The disintegrant α-cellulose or maize starch (for comparative studies) was incorporated intragranularly or extragranularly. The tablets were prepared by a wet granulation technique and then exposed to relative humidities (RH) 1%, 78% and 100% at an ambient temperature of 28 to 30°C for various time intervals up to 2 weeks. They were evaluated for disintegration time, hardness and moisture uptake. Tablets stored under RH % and 78% disintegrated within 15 minutes while those containing α-cellulose stored at RH 100% for a period ≥ 24 h failed to disintegrate within 60 minutes. The time taken for this conversion from disintegrating to non-disintegrating tablets varied with disintegrant concentrations and its mode of incorporation. Tablets containing maize starch did not display this moisture effect. The observation is thought to relate to the gelling of the α-cellulose particles upon moisture sorption. Thus, high relative humidities impair the disintegrant property of α-cellulose, which underlines the need to prevent such tablets from moisture.

Keywords: α-cellulose; disintegrant property; humidity effect; internal; external disintegrants

The polymer α-cellulose is that part of cellulose materials which is insoluble in 7.5% w/w solution of sodium hydroxide at 20°C (1). This property distinguishes it from β- and γ- celluloses. It is obtained from wood pulp (2) or more recently from agricultural wastes such as maize cob, rice husk or groundnut shell (3, 4). It has potentials in tablet formulations as a disintegrant and as a direct compression base (3). In the latter application the α-cellulose probably undergoes thermomelting as a thermoplastic during compression to form welded bonds upon withdrawal of the applied load which accounts for the formation of hard tablets. However, its property as a thermoplastic is yet to be determined. The polymer α-cellulose is readily hydrated being capable of absorbing approximately four and a half times its own weight of water, care should therefore be taken if the cellulose is to be formulated as diluent with hydrolysable drugs such as aspirin (3). Its swelling ability is its greatest asset as a disintegrant in tablet formulations (4). Swelling of the α-cellulose inside the tablet causes localized stress which leads to tablet rupture (3). The hydrophilic swelling property of α-cellulose has also been exploited in controlled drug release from matrices which are non-disintegrating tablets (5, 6).

An aspect, which has not been considered, is the ability of celluloses to form gels as observed in our laboratory during preliminary studies at ambient temperatures upon slow hydration. When this occurs, the cellulose may be expected to lose its disintegrant property and may, in fact, act as a wet binder. In the tropics, the relative humidity is high virtually throughout the year, hence in this study the effect of high humidities on the disintegrant property of α-cellulose was investigated.

EXPERIMENTAL

Materials

The polymer α-cellulose was used as the test disintegrant. It was obtained locally as a fine white powder of irregular shaped particles from an agricultural waste – maize cob by sodium hydroxide and a sodium sulphite digestion process already described in detail elsewhere (3). Its physicochemical properties include a bulk density of 0.42 ± 0.01 g cm^{-3}, true particle density 1.56 ± 0.02 g cm^{-3}, particle size 38 ± 4.3 μm, pH of 10% dispersion in water 6.5 ± 0.3, loss on drying 6.2%, sulphated ash 0.1%, angle of repose 40.6° and it is readily hydrated taking up to four and half times its own weight of water (3). Maize starch (BP grade) was also used as disintegrant in comparative study. When used as an extragranular disintegrant both the α-cellulose and maize starch were dried immediately before incorporation into the granules. Paracetamol powder BP (Pharmaceutical grade) was used as the test drug. It was selected for the study because it forms poorly disintegrating tablets on its own (i.e. without disintegrant).

Granulation technique

A sample of the paracetamol powder (65 g) was wet – massed with 30 ml of starch mucilage

(20% w/v). The wet mass was pressed through a sieve of aperture size 1.4 mm, spread thinly on trays and then dried at 50°C for 1 h in a hot air oven (Kottermann, Germany). The half dried mass was pressed through a sieve of aperture size 710 μm and dried finally at 50°C for 2 h to a moisture content of 2.1 ± 0.3% w/w. The desintegrants were incorporated intragranularly or extragranularly at concentrations of 1% to 5% w/w. Intergranular incorporation meant that the disintegrant was mixed with the drug powder before wet granulation while extragranular incorporation meant that the dried disintegrant was blended with the preformed granules immediately before compression.

Preparation of tablets

The granules were compressed with a single punch machine (Manesty, type F_3) to form flat-faced tablets of weight 550 mg ± 2.2 mg, diameter 12.5 mm and thickness 3.38 mm ± 0.2 mm. The tablets were compressed at a pressure of 27.5 (arbitrary unit on the load scale). Tablets of paracetamol without disintegrant were formed and used as control. Tablets were stored for 24 h in a desiccator containing dried silica gel before their evaluation.

In another aspect of the study, tablets which had been exposed to high humidity (RH 100%) for 24 h were dried at 50°C for 3 h in a hot air oven to a mean moisture content of 1.95 ± 0.15% w/w and re-evaluated for disintegration times and hardness. The aim was to investigate whether drying will reverse the moisture effect on the tablet.

Evaluation of the tablets

Disintegration test

The disintegration test was carried out using the British Pharmacopoeia method (7). Six tablets were used for each determination and the mean reported. Tablets that failed to disintegrate within 60 min were regarded as non-disintegrating tablets as such tablets did not disintegrate even when observed for a further 5 h. The time taken for the tablets to transform from a disintegrating to non-disintegrating statues was noted.

Test for moisture effect on the particle structure of the disintegrant powders

Moisture effect on the particle structure was investigated by photomicroscopy. Samples of the disintegrant powders were dried at 50°C for 3 h in a hot air oven and powdered in a dried mortar. The powdered samples were spread thinly on microscope slides which were stored, some in a desiccator containing dried silica gel (RH 1%) and others in a humidity chamber (RH 100%) for 24 h at ambient temperature 28 to 30°C. After these exposures, the slides were examined for any changes in particle structure such as enlargement and fusion to a coherent mass with a light microscope. The experiment was carried out in triplicates. Photomicrographs of representative samples were taken at a magnification of × 40.

Hardness test

This was measured using a Monsanto hardness tester. 10 tablets were used in each determination (8). The test was determined for tablets stored under different conditions of relative humidities.

Storage conditions of the tablets

Tablets used in the disintegration and the hardness test were stored under different relative humidities, namely 1%, 78% and 100%. The tablets were exposed to these humidities for selected time intervals up to a maximum of 2 weeks. Beyond this point microbial degradation of the tablets may occur. To obtain the relative humidity of 1%, a glass chamber was charged with a dried silica gel. A relative humidity of 78% was generated by placing a supersaturated solution of sodium chloride (NaCl) in a glass chamber while a relative humidity of 100% was obtained by placing distilled water in the glass chamber. The temperature in each of these chambers was between 28 to 30°C. Samples of the tablets (20) were kept in each of these chambers for selected time intervals before their evaluation for disintegration time and hardness as described above.

Moisture uptake experiment

Tablets with varied concentrations of the disintegrants were stored under a relative humidity of 100%. The initial tablets weight (M_0) and the weight after exposure to moisture for time t (i.e., M_t) were determined. The % moisture uptake (w/w) was calculated from the expression $\frac{M_t - M_0}{M_0} \times 100\%$ and was taken as thedegree of hydration. The test was limited to a relative humidity of 100% because it was only under this condition that the transformation from disintegrating to non-disintegrating tablets was observed.

RESULTS

Disintegration profile of the tablets

Tablets consisting of paracetamol without disintegrants did not disintegrate when observed for 60 minutes and above. Exposure of these tablets to R.H of 100% did not modify the disintegration profile of these tablets. Inclusion of the disintegrant α--cellulose or maize starch 1% w/w to 5% w/w in the

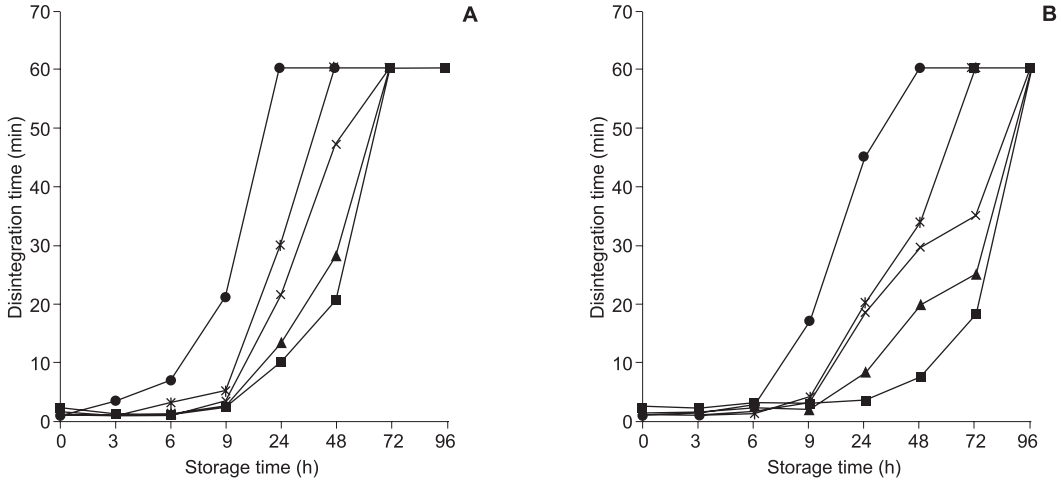

Figure 1. Changes in the disintegration time of the tablets containing α-cellulose as disintegrant during storage at a relative humidity of 100% and at a room temperature of 28 ± 2°C. Disintegrant concentrations in the tablets (% w/w) were 1% (■), 2% (▲), 3% (X), 4% (∗), 5% (●); mode of incorporation (A) intragranularly; (B) extragranularly.

Table 1. Time of conversion to non-disintegrating tablets as affected by disintegrant concentration and mode of incoporation

Disintegrant conc. (% w/w)	Time of conversion (h) in tablets containing the disintegrant:	
	Intragranular	extragranular
0	–	–
1	72	96
2	72	96
3	72	96
4	72	72
5	24	48

(–) = no conversion

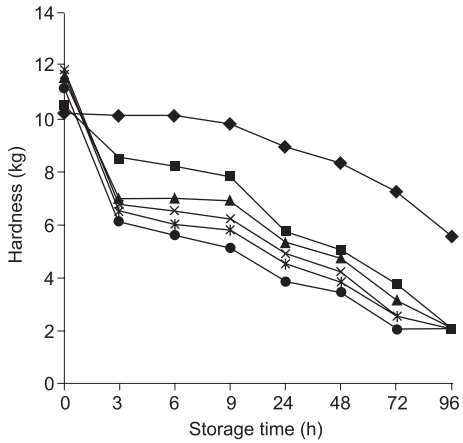

Figure 2. Effect of moisture uptake on the hardness profile of the tablets containing α-cellulose as disintegrant at a relative humidity of 100%. Disintegrant concentrations in the tablets (% w/w) were: 0% (◆); 1% (■); 2% (▲); 3% (X); 4% (∗); 5% (●).

Table 2. Differences in moisture uptake (degree of hydration) of tablets containing α-cellulose or maize starch as disintegrant

Storage time (h)	Moisture uptake (% w/w) in the tablets containing 5% disintegrant: intragranular	
	α-cellulose	maize starch
24	2.13	1.70
48	2.25	1.85
72	3.05	1.98
96	4.32	2.15
120	4.52	2.45

tablets by intragranular incorporation drastically reduced the disintegration time. For instance, the disintegration time of tablets containing 1% w/w α--cellulose was 2.0 min and 5% w/w was 0.7 min. The corresponding values for tablets containing the same concentration of maize starch were 2 min (1% w/w) and 0.5 min (5% w/w). Hence, there was no obvious difference in the performance of the two disintegrants. The mode of incorporation did not also affect the disintegration profile significantly. For instance, at 5% w/w α-cellulose the disintegration time of the tablets were 0.70 min (intragranular) and also 0.74 min (extragranular).

Tablets stored under relative humidities 1% and 78% did not display any marked changes in the

disintegration profile when observed over the period of 2 weeks. However, tablets exposed to a relative humidity of 100% for ≥ 24 h displayed a sharp increase in disintegration time (Figure 1). The tablets actually became non-disintegrating having failed to disintegrate within 1 h. This effect was observed only in tablets containing α-cellulose while those containing maize starch readily disintegrated within 15 min even after their exposure to moisture. In the case of the α-cellulose tablets, the observed moisture effect was more marked in tablets containing the internal disintegrant compared with those containing external disintegrant (see Figures 1a & b). For instance, the time taken for the conversion to non-disintegrating form was 24 h in the case of tablets with the intragranular disintegrant and 48 h in the case of

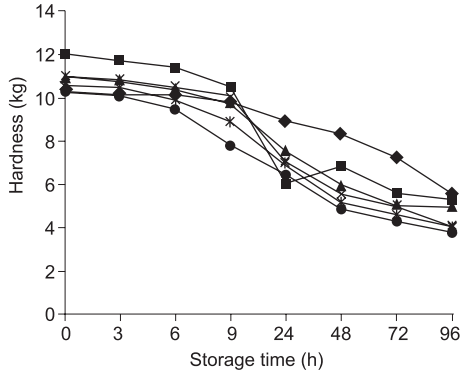

Figure 3. Effect of moisture uptake on the hardness profile of the tablets containing maize starch as disintegrant at a relative humidity of 100%. Disintegrant concentrations in the tablets (% w/w) were: 0% (◆); 1% (■); 2% (▲); 3% (X); 4% (∗); 5% (●).

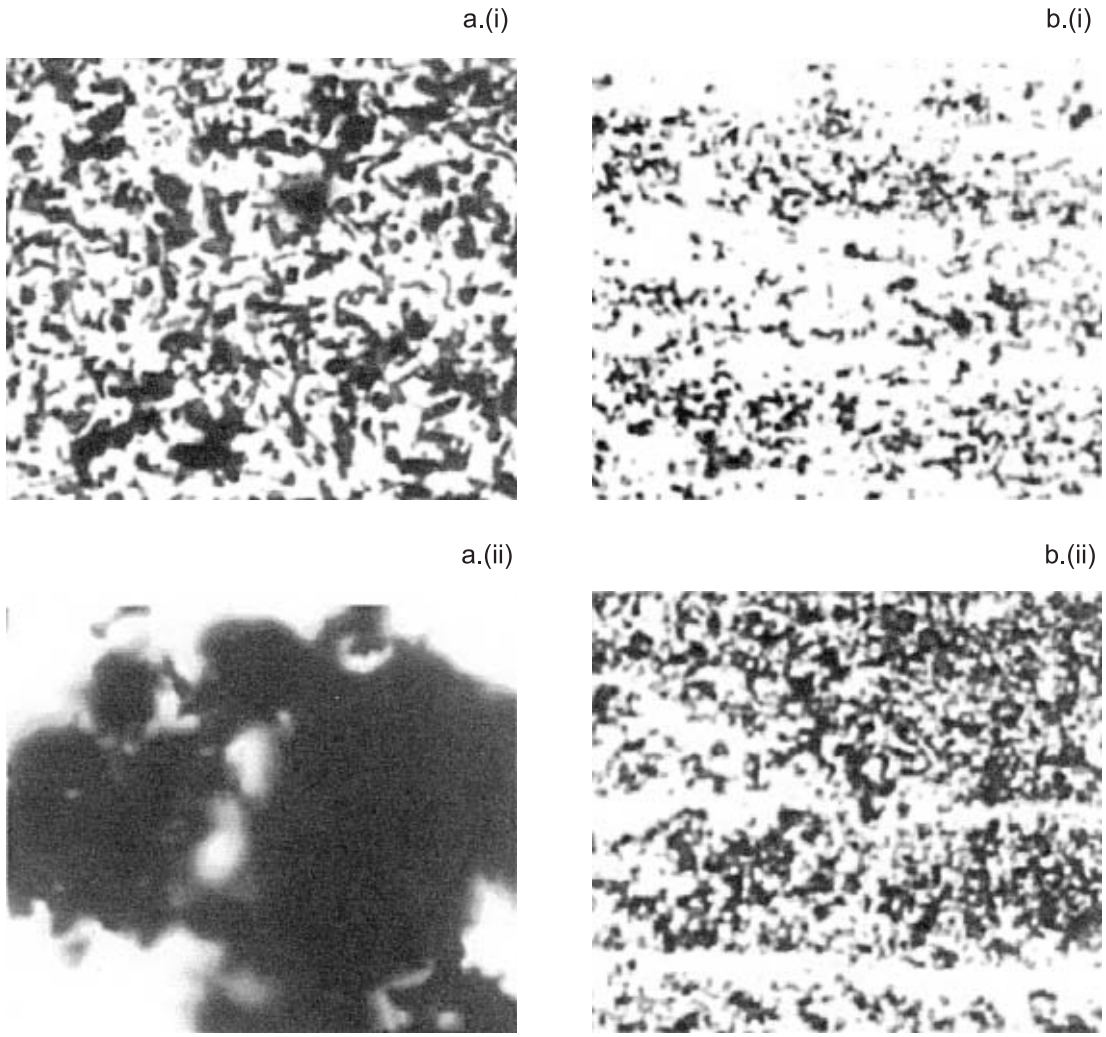

Figure 4. Photomicrographs of α-cellulose particles stored in desiccator (RH 1%) for 24h (a.i) and those stored in a humidity chamber (RH 100%) for 24h (a.ii) and the photomicrographs of maize starch particles similarly stored in a desiccator (b.i) and in a humidity chamber (b.ii): magnification x 40.
Note: Swelling and fusion of particles to form a coherent mass in (a.ii).

tablets with the extragranular disintegrant. The rate of conversion was also determined by the α-cellulose concentration in the tablets. The conversion was slower as the disintegrant concentration deceased (Table 1).

Hardness and moisture uptake profile of the tablets

The tablets generally became softer during storage when exposed to moisture at RH 100%. This effect was greater in tablets containing α-cellulose as disintegrant compared with those of maize starch (Figures 2 and 3). Tablets of the α-cellulose showed a higher potential for moisture uptake (i.e. the degree of hydration) compared with those of maize starch (Table 2). The degree of hydration of tablets containing α-cellulose was almost twice that of maize starch.

Drying of the tablets after previous exposure to moisture increased tablet hardness. For example, tablets containing 5% w/w of α-cellulose gave hardness of 1.0 kg and 7.0 kg before and after drying respectively.

Moisture effect on the particle structure of the disintegrant powders

The photomicrographs of samples of α-cellulose powder stored in a desiccator for 24 h showed discreate particles, which were mainly elongated fibres (Figure 4a(i)). On the other hand, photomicrographs of samples exposed to moisture (RH 100%) revealed that the α-cellulose particles had swelled and fused to a coherent mass, indicative of gelling (Figure 4a(ii)). In the case of maize starch, their exposure to moisture caused slight swelling of the particles but did not fuse or gel as was the case with the α-cellulose particles (see Figure 4b(i) & (ii)).

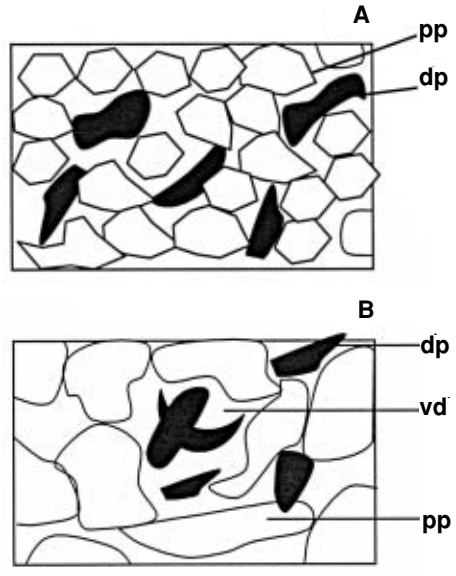

Figure 5. Model for the particle distribution of disintegrant incorporated (A) intragranularly or (B) extragranularly, note that most of the disintegrant particles were collected in the inter granular void spaces.
dp = disintegrant particles
pp = paracetamol particles witch can be fine in (A) and granules in (B)
vd = void space

DISCUSSION

Mechanism for impairment of the disintegrant property of α-cellulose

The failure of the tablets to disintegrate after their exposure to a high humidity of 100% suggests that the disintegrant property of α-cellulose was impaired. The gelling of α-cellulose particles upon moisture sorption implies that the polymer swelled upon hydration. The swelling was a slow process since the tablets did not disintegrate during their exposure to moisture. Another evidence that supports this view is that the tablets took a minimum of 24 h to become non-disintegrating. Already gelled by this slow process of hydration, the ability of the α-cellulose to further swelling when the tablets are placed in a disintegration fluid will be compromised. It is for this reason that disintegrants are dried immediately before use in tabletting.

Factors such as microbial degradation and ageing effect may denature the polymer. These considerations are, however, unlikely in the present study because the change in the disintegration characteristics of the tablets can be elicited in 24 h when any microbial or ageing effect will not be appreciable.

Explanation for the observed anomalous relationship between tablets hardness and disintegration time

The results show that the tablets became softer, but with prolonged disintegration time after their exposure to moisture, which is anomalous because only hard tablets are associated with long disintegration times (3). This anomaly is attributable primarily to the impairment of the disintegrant property of the α-cellulose already noted above. In addition, the conversion of the α-cellulose to a gel may provide a wet binder effect, which implies a greater resistance to tablet rupture. Drying of the tablets after their initial exposure to moisture did not reverse the non-disintegrating status of the tablets perhaps because the α-cellulose became a xerogel during drying of

the tablets. Xerogels are known to impact binder effect as reflected by the observed increase in tablet hardness after drying.

Explanation for the greater susceptibility of intragranular disintegrant to moisture

The greater susceptibility of tablets containing internal disintegrant to moisture compared with tablets containing the extragranular disintegrant probably relates to the differences in the distribution of the disintegrant powder within the tablet. In the case of the intragranular incorporation, the α-cellulose particles will be uniformly and finely dispersed among the fine particles of the drug thus giving a large surface area to the disintegrant powder for moisture sorption. On the other hand, extragranular incorporation of the disintegrant powder will fill and concentrate more easily into intergranular void spaces upon compression of the granules/disintegrant powder blend. This will lead to formation of few but large particles of the disintegrant with a consequent reduction of their surface area available for moisture sorption. This model of particle distribution is illustrated in Figure 5 where the paracetamol particles are in the form of fine powder in (A) and granules in (B). The shape and size of the particles reflected in the model were as seen under the microscope at magnification of × 40.

CONCLUSIONS

The results of the study permit the following conclusions. Firstly, high relative humidities as may be encountered in the tropics impair the disintegrant properties of α-cellulose thus emphasing the need to protect such tablets from moisture. Secondly, tablets containing intragranular compared to extragranular disintegrant are more susceptible to this moisture effect. On this basis extragranular incorporation is preferred. Thirdly, the observed conversion of the tablets to non-disintegrating forms may be exploited in prolonged released formulations.

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