Effect of Humidity on the Disintegrant Property of α-Cellulose, Part II: A Technical Note

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INTRODUCTION

The polymer, α-cellulose, is a fibrous residue obtained by delignification of wood pulp[1] or more recently from agricultural wastes such as groundnut shells, rice husks, and maize cobs.[2-4] α-Cellulose differs from β- and γ-cellulose by being insoluble in 17.5% wt/vol sodium hydroxide solution. It is a fluffy powder with a bulk density of 0.36 g/cm^{-3}, true particle density of 1.59 g/cm^{-3}, and porosity 0.77.[4] It is a poorly flowing powder with angle of repose up to 45°C.[2] Nevertheless, it exhibits plastic compression[5] and may therefore be explored as a direct compression base, thus displaying similar property as low crystallinity celluloses[6] and the well-known microcrystalline cellulose. It hydrates readily, absorbing up to 4.5% of its own weight of water.[2] This aqueous swelling property is its major asset as a disintegrant in tablet formulations. Thus, the disintegrant property of α-cellulose sourced from agricultural wastes such as groundnut shells, rice husks, and maize cobs has been investigated in previous studies.[2-4] The outcome was that α-cellulose is an effective disintegrant in various tablet formulations. However, accelerated stability studies[7] suggested that moisture uptake would have the potential to impair the disintegrant property of α-cellulose in tablet formulations. Paracetamol tablets were used in that study and gelling of the α-cellulose powder was proposed as the possible mechanism for the humidity effect.

In order to explore the general nature of the finding and to lend support to the gelling mechanism, the study is here extended to other drugs differing in their moisture uptake potentials (ie, hygroscopicity) and aqueous solubility from paracetamol; these include aspirin (a hygroscopic drug) and chloroquine phosphate (a water-soluble drug). Drugs with a higher moisture uptake capacity will be expected to be more prone to impairment of tablet disintegration time (by promoting gelling of the α-cellulose), while a higher aqueous solubility of the drug will tend to ameliorate the moisture effect by creating pores in the tablet as the drug dissolves out to facilitate disintegration. These aspects were investigated in the present study by comparing the moisture effect on the disintegration profiles of these various tablets.

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MATERIALS AND METHODS

The α-cellulose used in this study was extracted from maize cobs by alkaline digestion process[2] and was the test disintegrant. It is a white fibrous powder; its physical characteristics have been given above. The test drugs, aspirin, chloroquine phosphate, and paracetamol, were all British Pharmacopeial (BP) grade, supplied by BDH (Poole, UK) and were received as powders. They were selected for the study because they differ in their aqueous solubility and/or hygroscopicity.

Granulation and Tableting

Granules of aspirin were formed by slugging (ie, a precompression granulation), while those of chloroquine phosphate and paracetamol (100 g each) were formed by wet massing with starch mucilage (10 mL, 20% wt/vol). In all cases, the disintegrant powder was incorporated intragranularly, 5% wt/wt. This means that the disintegrant was dry-mixed with the drug powder prior to granulation. This mode of incorporation promotes disintegration of the tablets to finer particles compared with extragranular incorporation, whereby the disintegrant is added to the preformed granules.[8] The final tablet composition consisted of the drug (paracetamol or chloroquine phosphate) 91% wt/wt, binder 2% wt/wt, lubricant 2% wt/wt, and disintegrant 5% wt/wt, while the aspirin tablets consisted of 93% wt/wt, lubricant 2% wt/wt, and disintegrant 5% wt/wt. A lubricant (magnesium stearate) was added to the aspirin and paracetamol granules, but this was not suitable for chloroquine phosphate as the granules formed a sticky mass when this lubricant was added. Hence, in this case, stearic acid was substituted for magnesium stearate.

Samples of the granules (500 mg) were each compressed to flat-face tablets using a single punch machine (type F_3, Manesty, Liverpool, England, UK) at a load 27.5 (arbitrary units on the load scale). The machine was manually operated. The maximum load was held on the tablet for 30 seconds to allow time for consolidation. The tablets were

stored in a dessicator for 24 hours to equilibrate before their evaluation.

Determination of Tablet Packing Fraction (P_f)

The tablet packing fraction (P_f) is a measure of the degree of consolidation or compactness of the tablet. It is given by the following expression[9]:

$$P_f = w/\pi r^2 t\rho, \quad (1)$$

where w is the weight of a tablet of radius, r, and thickness, t, and ρ is the particle density. The tablet radius and diameter were determined using a digital micrometer. Ten tablets were used in each measurement. The apparent particle density of the drug powder was determined using a fluid (liquid paraffin) displacement method, details of which have been described elsewhere.[10] Essentially, the weight of a specific gravity (SG) bottle filled with liquid paraffin and the weight of the SG bottle containing a sample of the drug powder (1 g accurately weighed) and then filled with liquid paraffin were determined. The data were used to estimate the volume of liquid paraffin displaced, which was taken as the volume of drug sample. The determination was performed in triplicate, and mean results were used in the calculation of P_f.

Moisture Uptake Experiments

In the first part of this study,[7] we reported that moisture uptake by paracetamol tablets (with α-cellulose [5% wt/wt] as disintegrant) did not display any appreciable moisture uptake or changes in their hardness and/or disintegration profiles when they were stored under relative humidity (RH) 1% and 78% for 2 weeks, except at RH 100%. This does not mean that the physical properties (hardness and disintegration times) of the tablets would not change if the tablets were exposed to the RH 78% for a long enough period (eg, over 12 months) to pick up sufficient moisture. Since it is not experimentally convenient to examine the tablets for that length of time, an exaggerated RH of 100% was selected in the present study for measuring the moisture uptake and its effect within 24 hours (ie, accelerated stability testing). In the procedure, a humidity chamber was created by placing a beaker of distilled water in a glass chamber giving an RH of 100% at the ambient temperature 30°C. The weight of the tablets (previously equilibrated in a dessicator for 24 hours) was individually determined using a sensitive electronic balance (Mettler Toledo B154, Greifensee, Switzerland) and then placed in the humidity chamber for various time intervals up to a maximum of 24 hours. At predetermined time intervals, the tablets were removed from the humidity chamber and reweighed. The percentage increase in weight was taken as the moisture uptake. Different humidity chambers were used for the different sampling intervals such that the tablets were not in contact with the external environment during the storage interval in the chambers.

Tablet Hardness and Disintegration Tests

The load-causing fracture (kg) of each of 10 tablets was determined with the Monsanto hardness tester (Monsanto Chemical, St Louis, MO).[11] The mean crushing load was taken as the tablet hardness. Tablet disintegration time (minutes) was determined following the method described in the *British Pharmacopoeia*.[12] Six tablets were used in each determination and the mean results reported. The tests were performed on the tablets before and after their exposure to the moisture as described in the "Moisture Uptake Experiments" section.

RESULTS AND DISCUSSION

The P_f values of the tablets (previously equilibrated in a dessicator) are presented in Table 1. The chloroquine phosphate and paracetamol tablets appeared to be slightly more compact than the aspirin tablets, but the difference was not statistically significant ($P > .05$). These data suggest that the various tablets were of similar porosity, and hence this porosity factor would not account for any differences in moisture uptake. Moisture uptake was comparatively higher in aspirin than in the chloroquine phosphate or paracetamol tablets, and the percentage moisture was similar in the chloroquine phosphate and paracetamol tablets (Figure 1 and Table 1). The higher uptake by aspirin tablets relates to the greater hygroscopicity of aspirin compared with chloroquine phosphate or paracetamol.

Moisture uptake affected the hardness and disintegration times of the tablets to different degrees. Chloroquine phos-

Table 1. Tablet Hardness, Packing Fraction, Porosity, and Moisture Uptake

Tablets	Hardness (kg)	Packing Fraction (P_f)	Porosity (1-P_f)	Moisture Uptake in 24 hours, % wt/wt
Aspirin	5.3 ± 0.2	0.95 ± 0.03	0.05 ± 0.002	3.4 ± 0.4
Paracetamol	11.5 ± 0.5	0.96 ± 0.01	0.04 ± 0.002	2.3 ± 0.5
Chloroquine	12.5 ± 0.3	0.96 ± 0.01	0.04 ± 0.003	1.9 ± 0.3

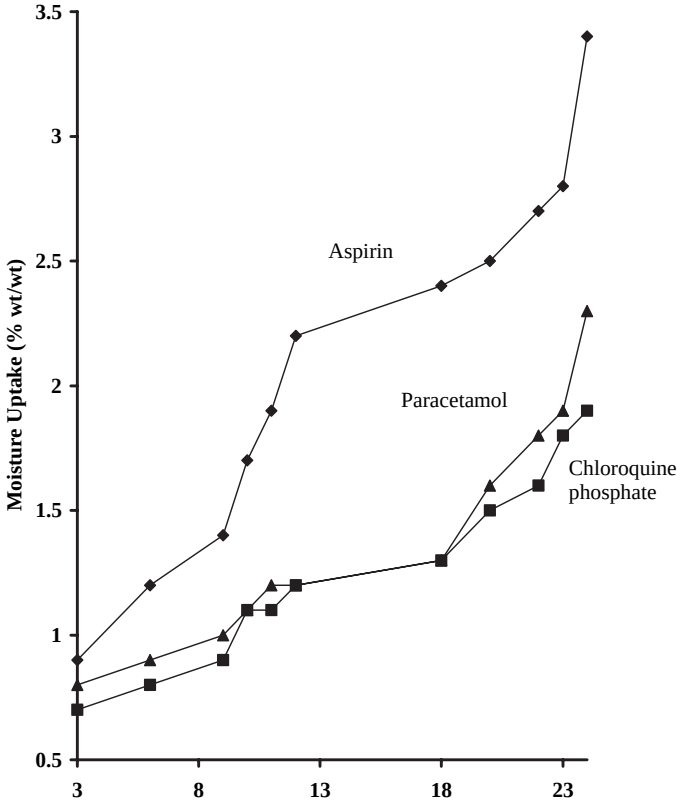

Figure 1. Moisture uptake potentials of the tablets exposed to RH 100% for various time intervals.

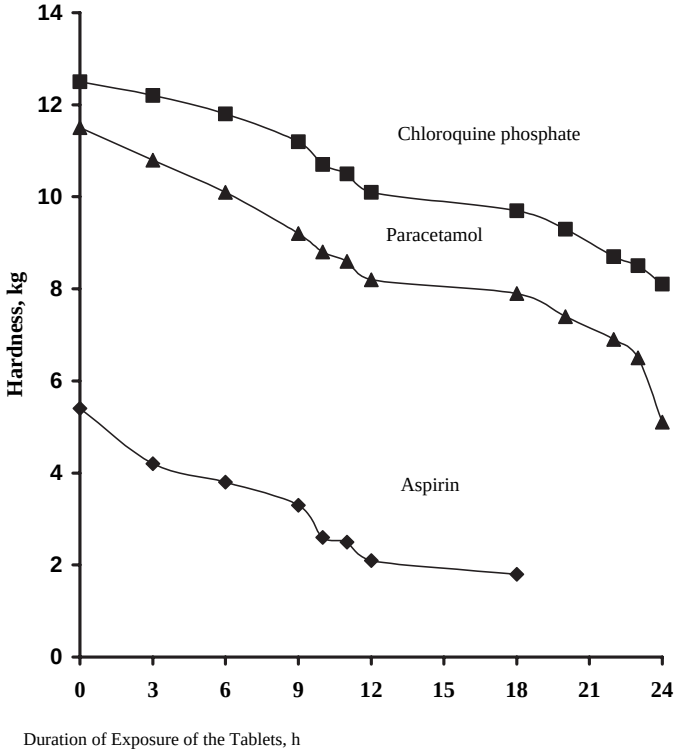

Figure 2. Changes in the hardness profiles of the tablets after their exposure to moisture for various time intervals. Note: Aspirin tablets became too soft after 18 hours of exposure, hence, the hardness could not be measured beyond this point.

phate and paracetamol formed harder tablets compared with aspirin; the chloroquine phosphate tablets were in turn slightly harder than the paracetamol tablets (Table 1). Upon exposure to moisture, the tablets generally became softer with time (Figure 2). The decrease in tablet hardness followed almost a linear fashion at the rates (kg h^{-1}) 0.20 (aspirin), 0.19 (chloroquine phosphate), and 0.21 (paracetamol), thus indicating that the rate of decrease in hardness was similar in the 3 types of tablets even though aspirin picked up moisture faster.

In spite of the decrease in tablet hardness, the disintegration times of all tablets increased considerably following their exposure to moisture. The extent of the increase depended on the duration of exposure and nature of the drug (Figure 3). Prior to the exposure, the aspirin tablets disintegrated rapidly within a minute, but after the exposure, their disintegration time increased rapidly until it reached 60 minutes after 9 hours of exposure. Beyond this point, the tablets failed to disintegrate even after 60 minutes, which is a matrix behavior.[13] Likewise, the paracetamol tablets disintegrated rapidly within a minute prior to their exposure to moisture, but after their exposure for 9 hours, disintegration time increased rapidly until it reached 60 minutes after 23 hours of exposure. Upon further exposure of the tablets to moisture beyond this point, the paracetamol tablets failed to disintegrate. In the case of the chloroquine phosphate tablets, disintegration time was initially up to 10 minutes prior to their exposure to moisture, probably because of the substitution of the more hydrophobic stearic acid for magnesium stearate as lubricant in the tablet formulations. Another probable reason was that chloroquine phosphate tablets were harder than aspirin and paracetamol tablets. Following their exposure to moisture, disintegration time of the chloroquine phosphate tablets increased steadily up to 22 minutes after 24 hours of exposure but did not attain the matrix (nondisintegrating) status as displayed by the aspirin and paracetamol tablets. This observation is attributable to the solubility of chloroquine phosphate in the disintegration medium. The dissolution of the drug will create pores in the tablet to facilitate disintegration. Aspirin tablets were more sensitive than the chloroquine phosphate and paracetamol tablets to the humidity because of their greater hygroscopicity as reflected by their higher moisture uptake, which will in turn facilitate the gelling of the α-cellulose particles in the tablet. The previous study showed that α-cellulose powder actually gelled when exposed to moisture for 24 hours,[7] which is the likely mechanism for the impairment of its disintegrant property.

Tablet disintegration time may increase during storage, and it is usually associated with a corresponding increase

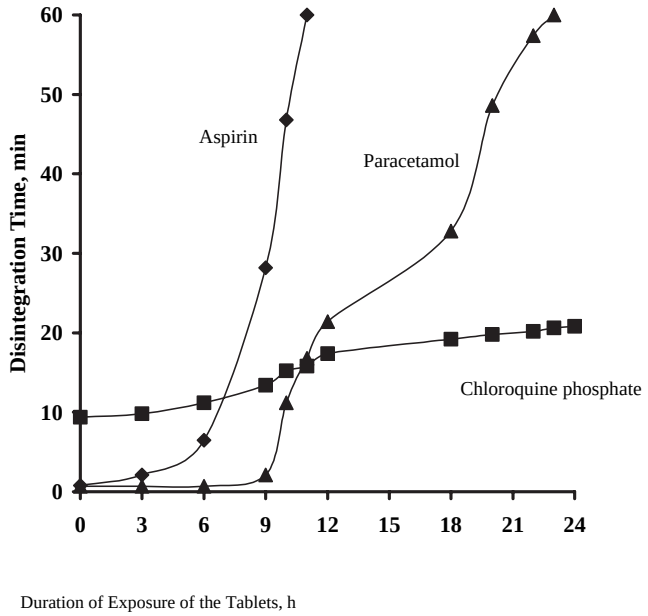

Figure 3. Disintegration profiles of the tablets after their exposure to moisture for various time intervals.

in tablet hardness. In this present study, however, tablet hardness actually decreased (Figure 2), while disintegration time increased (Figure 3) during storage of the tablets under a high humidity. The decrease in tablet hardness is due to hydration of the tablets with a consequent weakening of interparticulate bonding. However, such a decrease in tablet hardness was not accompanied by a corresponding decrease in disintegration time as expected, rather there was an increase. The explanation is that soft tablets were held in a gel matrix (ie, in a spongy polymeric network of the α-cellulose), thus preventing disintegration. Consequently, tablet disintegration time was determined by the extent of gel formation, rather than the change in tablet hardness. Hence, an increase in moisture uptake to promote gelling was associated with longer disintegration time of the tablets.

CONCLUSION

The summary is that the high humidity impaired the disintegrant property of α-cellulose in all 3 tablets tested. Tablets of aspirin, which is the more hygroscopic drug, were also more sensitive to the humidity effect, while tablets of chloroquine phosphate, which is a water-soluble drug, were the least sensitive to the humidity effect. The results permit the conclusion that moisture uptake with subsequent gelling of the α-cellulose is the mechanism of impairment of its disintegrant property. The tablets would not normally be stored under an RH as high as 100%, nevertheless, the results of the accelerated stability study have underscored the need to protect tablets containing α-cellulose as disintegrant from moisture.

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