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Factors affecting the disintegration and dissolution of chloroquine phosphate/starch tablets

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A study has been made of the effects produced on the disintegration and dissolution times of chloroquine phosphate tablets by varying their moisture and starch contents and the distribution of the starch in the formulation. 3 to 5% w/w of moisture produces a maximum in the disintegration and dissolution times. Starch added externally as a powder acts only as a disintegrating agent for the tablets, but starch added internally as a paste during granulation acts both as a binding agent and as a disintegrant.

Chloroquine phosphate is generally administered as tablets containing 250 mg of active drug with appropriate quantities of excipients. A common excipient for these tablets is maize starch and it is generally used in the concentration range from 10–30% w/w. It is incorporated both as a granulating agent (in the form of a paste), when it is described as 'internal starch' and it is also added as a dry powder to the finished granules, when it is described as 'external starch' (Higuchi, Elowe & Busse, 1954). Many chloroquine phosphate tablet formulations contain both internal and external starch. Nair & Bhatia (1957) have suggested that the external starch causes the tablets to distintegrate in water into granules which are then deaggregated by the internal starch into their constituent particles.

It is well known that the physical and mechanical properties of granules and tablets depend on the nature, particle size and composition of the formulation and on the process variables such as the method of granulation, volume of the granulating fluid, massing time, and method of compressing the granules into tablets (Higuchi, Rao & others, 1953; Ganderton & Hunter, 1971; Hunter & Ganderton, 1972, 1973; Chalmers & Elworthy, 1976; Esezobo & Pilpel, 1976; Kurup & Pilpel, 1977). The particular effects of moisture content on the mechanical properties of tablets have been studied amongst others by Shotton & Rees (1966), Armstrong & Griffiths (1970) and Esezobo & Pilpel (1976).

In the present work a detailed study has been made of the combined effects of moisture and the starch content, both internal and external, on the distintegration and dissolution characteristics of chloroquine phosphate tablets which had been compressed to a fixed packing fraction of 0·76, corresponding generally to manufacturing practice.

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MATERIALS AND METHODS

Materials

Chloroquine phosphate B.P. from ICI Pharmaceuticals Division and Maize starch B.P. from BDH were used.

Preparation of granules

Three types of chloroquine phosphate/starch granules were prepared containing 50% of the starch internally and 50% externally, type A; all the starch internally, type B; and all the starch externally, type C.

The type B granules were prepared in 500 g batches by mixing the required quantities of chloroquine phosphate in a Kenwood planetary mixer for 2 min, either with 150 ml of water (added incrementally) or with 150 ml of a well mixed slurry containing up to 30% w/w of starch in distilled, cold water, whichever was appropriate. The resulting doughs, containing between 0 and 30% w/w of starch, were pressed by hand through a No. 12 mesh sieve and the granules were spread on trays and dried at 60° for 16 h and then re-sieved through a No. 16 mesh sieve. Shorter drying periods were employed for the samples which were required to contain more than 4% w/w of moisture.

Batches of type C granules were prepared from the batch of type B granules which contained no internal starch, by intimately mixing in appropriate amounts of starch in the form of a fine powder. The same procedure was employed for preparing the type A granules, but this time the starch was added to the type B granules which already contained internal starch. The finished batches consisted of intimate mixtures of granules (850–1000 μm diam.) and starch powder (30 μm diam.). They were stored in well sealed jars and their moisture contents were periodically checked by their loss in weight on drying at 80° to constant weight.

Preparation of tablets

Approximately 300 mg of the granules were compressed at 0·22 mm s^{-1} in a 9·5 mm diameter stainless steel die fitted with normal concave punches using a hand press (Research and Industrial Instrument Co., London) and applying predetermined loads for 1 min. Before each compression, the faces of the die and punches were lubricated with a 1% w/w dispersion of magnesium stearate in ether–ethanol (1 : 1). After compression the tablets (designated in the same way as the granules as Type A, B or C) were ejected from the die at the same rate of 0·22 mm s^{-1} and were stored in well-sealed containers for 24 h to allow for hardening and elastic recovery. Their weights and dimensions were then accurately measured to within ±1 mg and ±0·1 mm and their packing fractions were calculated by employing the equation proposed by Kurup & Pilpel (1977).

Testing

The disintegration times of the tablets were measured in distilled water at 37 ± 1° in a Manesty disintegration tester by the B.P. (1973) method. The tablets were considered completely disintegrated when all the particles passed through the wire mesh. The dissolution rates were determined in 1 litre of standard pH 6 buffer solution (B.P. 1973) in a round-bottomed flask maintained at the same temperature, employing a 5 cm, two-bladed paddle fitted 2 cm below the surface of the liquid and a stirring speed of 50 rev min^{-1}. The dissolved chloroquine phosphate was assayed by absorbance at 343 nm with a Cecil CE 202 spectrophotometer.

All measurements were made in quintuplicate on individual tablets and the results given are the mean values whose standard deviations varied from 0·6–2·2 (for disintegration) and from 1·9–5·8 (for dissolution) depending on the amount of starch present in the tablets and on its distribution.

RESULTS

The disintegration results for the type A tablets were plotted as a function of packing fraction for all the samples at different moisture levels and the values at a fixed packing fraction of 0·76 (corresponding to the commercial product) were determined. These are given in Table 1. Representative graphs, one for tablets containing different quantities of starch and similar moisture levels (1·75 to 2·25% w/w) and the other for the tablets containing 10% w/w starch and different moisture levels are given in Figs 1 and 2 respectively. In general, the disintegration times were minimal when the packing fractions of the tablets were between 0·76 and 0·82.

Table 1. *Values of disintegration time and t 50 for type A tablets at packing fraction 0·76 containing different amounts of starch and moisture.*

Starch %	Moisture content % w/w	Disint. time (min)	t 50 (min)
0	2·2	9·4	47·7
	3·5	11·5	57·2
	4·7	12·6	70·7
	6·2	9·6	46·2
10	2·8	7·8	33·2
	4·2	9·2	48·5
	5·2	10·3	55·5
	7·0	5·7	22·0
20	2·2	5·0	18·2
	3·5	6·2	27·5
	5·8	8·0	37·5
	6·8	6·3	30·5
30	2·2	2·3	7·5
	4·2	3·3	11·2
	5·4	2·5	10·0
	6·2	1·9	5·7

The dissolution results were obtained in the form of plots of cumulative percentage chloroquine phosphate dissolved *vs* time and typical graphs for the type A tablets containing 20% w/w starch at different packing fractions are shown in Fig. 3. From these graphs, the values of t 50 (the time required for 50% of the chloroquine phosphate to be released) were calculated and are included in Table 1.

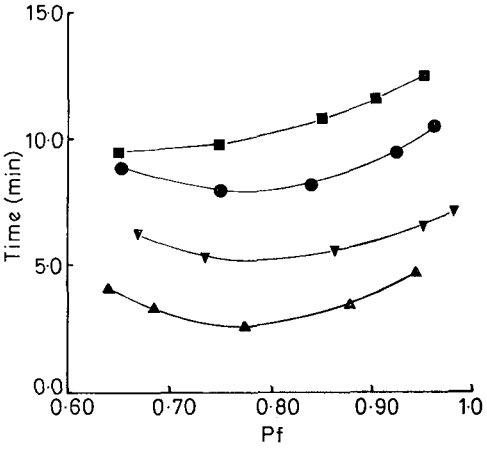

FIG. 1. Disintegration time (min) *vs* packing fraction (Pf) of type A tablets containing different quantities of starch and similar moisture levels (1·75 to 2·25% w/w). % w/w starch = ■, 0; ●, 10; ▼, 20; ▲, 30.

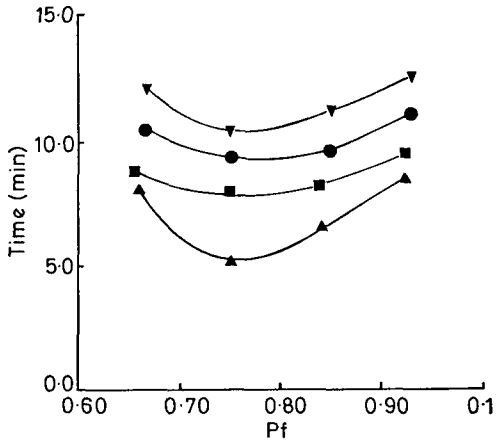

FIG. 2. Disintegration time (min) *vs* packing fraction (Pf) of type A tablets containing 10% w/w starch and different moisture levels. w/w moisture = ■, 2·8; ●, 4·2; ▼, 5·2; ▲, 7·0.

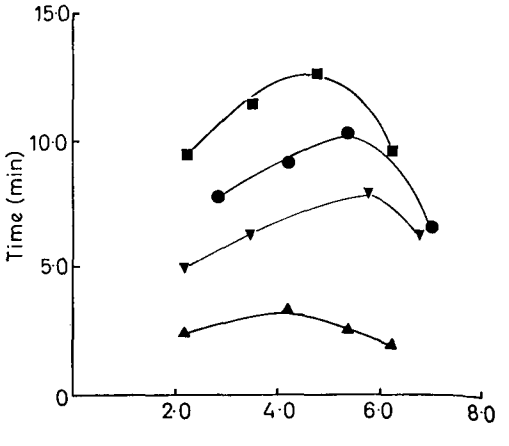

FIG. 4. Effect of moisture and starch on the distintegration time (min) of type A tablets at Pf 0·76. % w/w starch = ■, 0; ●, 10; ▼, 20; ▲, 30. Abscissa: Moisture content (% w/w).

Figs 4 and 5 show the way in which the values of disintegration time and t 50 of the type A tablets at a fixed packing fraction of 0·76 varied with moisture and starch content. (Similar results were obtained for other packing fractions). In general both the disintegration and dissolution times increased with moisture content attaining maxima at between 4 to 5% w/w moisture and then decreasing. A graph to illustrate the correlation between disintegration time and t 50 for these tablets is given in Fig. 6.

The dissolution profiles of type A, B and C tablets containing 10% w/w starch at Pf 0·76 are given in Fig. 7. The corresponding values of t 50 are listed in Table 2.

When the results were plotted on a larger scale and the slopes of the graphs over the first 30 min were examined in detail, it was found that quite large variations occurred from one type of tablet to another in the slopes, i.e. in the rates of dissolution in mg min^{-1}. This is illustrated in Fig. 8.

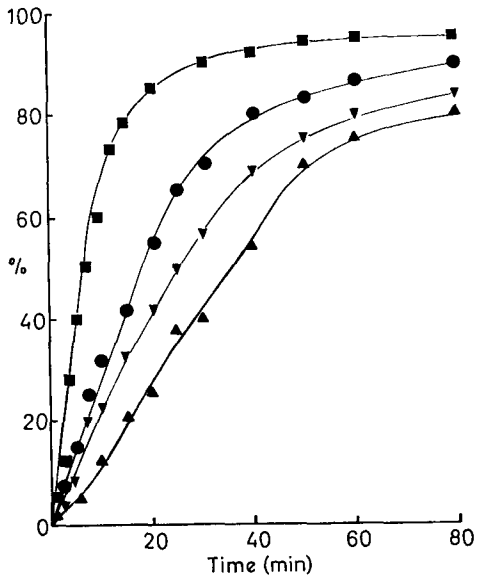

FIG. 3. Effect of packing fraction on the dissolution profiles of type A tablets containing 20% w/w starch. Pf = ■, 0·76; ●, 0·82; ▼, 0·87; ▲, 0·90. Ordinate: Cumulative % drug dissolved.

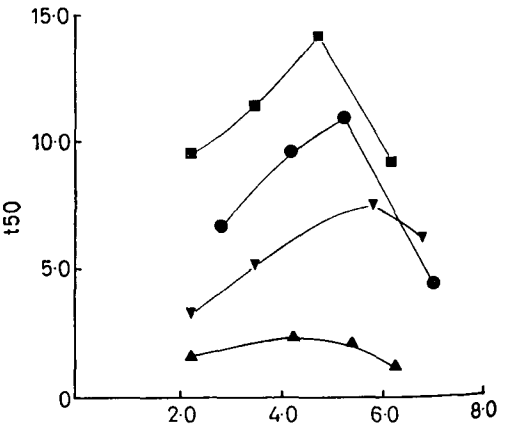

FIG. 5. Effect of moisture and starch content on t 50 of type A tablets at Pf 0·76. % w/w starch = ■, 0; ●, 10; ▼, 20; ▲, 30. Ordinate: t50 min. Absicissa: Moisture content (% w/w).

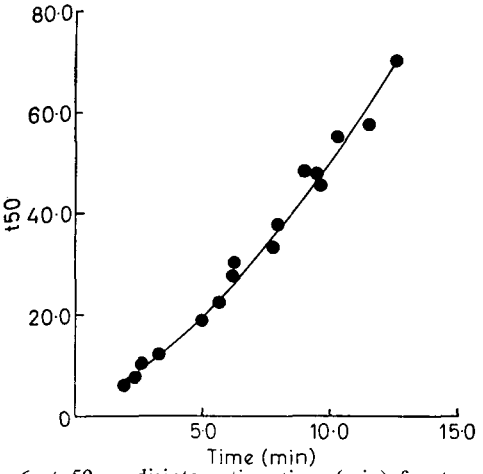

FIG. 6. t 50 *vs* disintegration time (min) for type A tablets at Pf 0·76. Ordinate: t50 min.

Following Wagner (1969) dissolution results can be plotted either as % drug dissolved on a probability scale *vs* log time or as log % drug undissolved *vs* time. The latter procedure tends to linearize results which would otherwise give curves and the resulting straight lines obey the simple dissolution equation

$$\log (W^{\infty} - W) = \text{Log } M - kt$$

$(W^{\infty} - W)$ is the amount of drug undissolved after lime t, k is the first order reaction rate constant and M is another constant which depends on the surface area available for dissolution and the solubility of the drug. Fig. 9 shows these plots for the type A, B and C tablets containing 20% w/w starch at a packing fraction 0·76.

Two types of plots were obtained depending on the total amount of starch present and its distribution in the tablets; either a single straight line of slope $-k_1$ or two straight lines with slopes $-k_1$ and $-k_2$. The values for the three different types of tablets containing either 10 or 20% w/w total starch are listed in Table 2.

Table 2. *Effect of distribution of starch on values of t 50 and rate constants.*

% Starch	Distribution	t 50 (min)	$-k_1 \times 10^2$ (min^{-1})	$-k_2 \times 10^2$ (min^{-1})
10	Internal	52·0	0·72	*
	Internal and external	25·0	1·92	*
	External	8·2	4·00	1·48
20	Internal	34·0	0·97	*
	Internal and external	12·5	3·33	0·98
	External	7·0	4·10	1·50

* A single straight line was obtained whence $k_2 = k_1$.

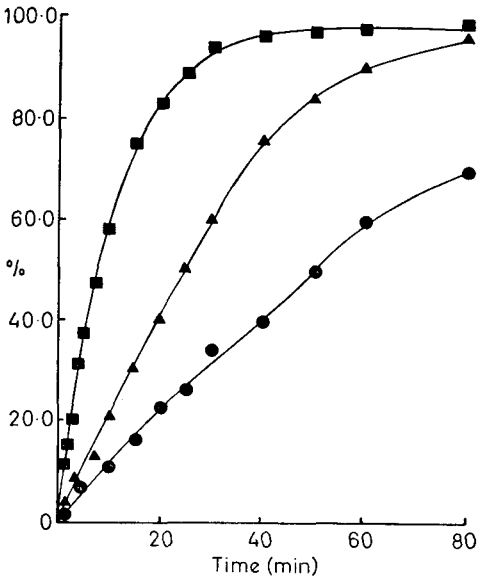

FIG. 7. The effect of distribution of starch on the dissolution profiles of tablets containing 10% w/w starch at Pf 0·76. ●, Type B (internal starch). ▲, Type A (internal and external starch). ■, Type C (external starch). Ordinate: Cumulative % drug dissolved.

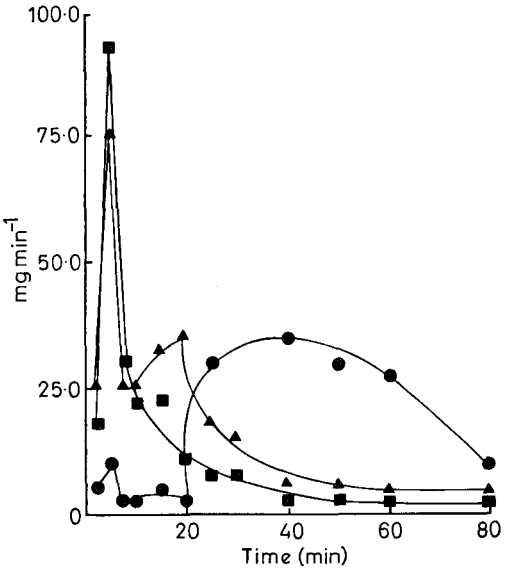

FIG. 8. Dissolution rates *vs* time for tablets containing 20% w/w starch at Pf 0·76. ●, Type B (internal starch). ▲, Type A (internal and external starch). ■, Type C (external starch). Ordinate: Drug dissolved (mg min^{-1}).

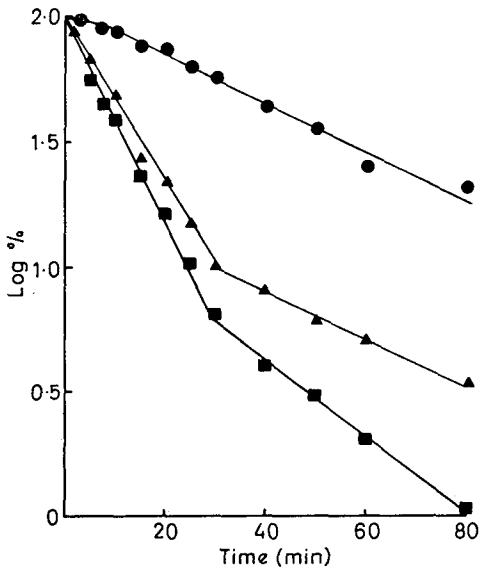

FIG. 9. Log % drug undissolved *vs* time for the tablets containing 20% starch at Pf 0·76. ●, Type B (internal starch). ▲, Type A (internal and external starch). ■, Type C (external starch). Ordinate: Log % drug undissolved.

DISCUSSION

The plots of disintegration and dissolution (t 50) times *vs* packing fraction for all the samples examined exhibited minima at packing fractions between about 0·7 and 0·85. This has been noted by others (Polderman & Braakman, 1968; Esezobo & Pilpel, 1976; Kurup & Pilpel, 1977) and has been explained in terms of the effects that the packing fraction has on (1) the specific surface area of the particles, (2) the rate of penetration of liquid into the interior of the tablets and (3) the pore space in which particles of starch can swell when wetted by water before disrupting the tablets.

The addition of starch to the chloroquine phosphate produced more or less parallel decreases in both the disintegration and dissolution times of the tablets (see Figs 4 and 5). Although the subject has been studied extensively, there is still uncertainty on how exactly the starch acts as a disintegrant. Some authors (Fakouhi, Billups & Sager, 1963; Billups & Cooper, 1964; Patel & Hopponen, 1966) consider that the penetration of water causes the starch grains to swell and so disrupt the tablets. Others (Curlin, 1955; Borzunov & Shevchenko, 1967; Ingram & Lowenthal, 1968; Manudhane, Contractor & others, 1969) believe that the presence of starch increases the capillarity of the powder formulation thus facilitating the uptake of water. However there are many substances that swell to a greater extent than starch but are nevertheless poor disintegrants. Many semipolar and nonpolar fluids penetrate tablets yet do not cause them to disintegrate (Nogami, Nagai & Uchida, 1966; Patel & Hopponen, 1966). Moreover, certain tablets disintegrate rapidly even though their capillarities are very low (Bánó, Szarvas & Aradi, 1961; Patel & Hopponen, 1966; Wood, 1967). It is therefore probable that the starch produces its disintegrating effect by several different mechanisms, depending on the particular formulation concerned.

The results in Table 1 and Figs 4 and 5 showing that the disintegration and dissolution times of the chloroquine phosphate tablets increased with moisture content of the granules and attained maxima at about 4–5% w/w moisture are consistent with previous observations. Krowczynski, Kolarski & Swoboda (1968) for example showed that if the moisture content of starch was increased beyond a certain level, its swelling action diminished due to a reduction in its capacity to absorb further moisture.

Alternatively, during granulation, the starch may be distributed as a thin film around the granules. When finished tablets are placed in water, the layer of starch could form a mucilagenous viscous barrier (Huber, Dale & Christenson, 1966) and this would retard disintegration and dissolution of the drug. The magnitude of the effect would be expected to depend on the initial moisture content of the starch.

Up to about 5% w/w concentration, moisture in granules and tablets is thought to be in the pendular, funicular and capillary states and increasing the moisture produces an increase in their tensile strength (Pilpel, 1969). This can be expected to be accompanied by an increase in the disintegration and dissolution times. However more than this amount of moisture begins to act as a dispersion medium, reducing the cohesive forces between the particles (Derjaguin, 1961) and leading to the observed decrease in the disintegration and dissolution times (see Figs 4 and 5).

For all samples investigated there was a direct correlation between the disintegration time and the time required for 50% of the chloroquine phosphate to dissolve. Similar relations have been reported by Schroeter, Tingstad & others (1962) and by Esezobo & Pilpel (1976); but the numerical terms in these relations depend considerably upon the drug and on the excipient involved.

On coming into contact with water, a tablet disintegrates into granules and then deaggregates into fine particles. Dissolution thus occurs from intact tablet, granules and fine particles. Assuming

that the dissolution rate is proportional to the surface area available, the amount dissolved from the intact tablet will be negligible compared with that dissolved from the granules and fine particles. Hence disintegration is the rate determining step in the dissolution process and it is to be expected that t_{50} will show a direct correlation with the disintegration time.

Figs 7 and 8 and Table 2 show that the dissolution characteristics of the present tablets varied with the distribution of starch in the granules. When the starch was all external (either 10 or 20% w/w) the dissolution rate increased initially very rapidly and then tailed off. This is because, without any internal binding agent, the tablet breaks up immediately into fine particles producing a large surface for dissolution. In contrast, tablets containing only internal starch (either 10 or 20% w/w) initially dissolved slowly by erosion from the surface of the intact tablet. The rate then increased gradually to a maximum when the tablet disintegrated and then decreased. Tablets containing both internal and external starch followed an intermediate pattern, initially disintegrating into granules which then de-aggregated into fine particles. This accounts for the occurrence of the two peaks in the particular graph of dissolution rate *vs* time in Fig. 8.

The distribution of the starch in the tablets also affected the shapes of the Wagner plots obtained (Fig. 9). Tablets containing only internal starch and up to 10% w/w of internal and external starch gave single straight line plots showing that the dissolution obeyed pseudo-first order kinetics. In contrast, the tablets containing only external starch or 20% w/w internal and external starch gave graphs consisting of two straight lines.

In deriving his equation Wagner assumed that the rate of dissolution was proportional to the surface area generated and that the surface area would increase with time, eventually reaching a maximum and then fall off progressively to zero. However, it is evident from the present results, Figs 8 and 9, that the dissolution of chloroquine phosphate/starch tablets is very dependent both on the quantity and on the distribution of the starch in the formulation.

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