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A NEW COMPUTER-AIDED APPARATUS FOR SIMULTANEOUS MEASUREMENTS OF WATER UPTAKE AND SWELLING FORCE IN TABLETS.

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SUMMARY

Water uptake and disintegrating force development have frequently been related to tablet disintegration properties.
Water penetration into compressed tablets has been studied by many authors using modified Enslin apparatus. Meanwhile, in previous papers by our group, a great deal of attention has been paid to the measurements of disintegrating force and to the kinetics of force development.

Given the fact that water penetration and swelling force development are related to each other, a new apparatus was set up which allows simultaneous measurements of water penetration and force development. It consists of a modified apparatus for force measurements, integrated with a modified Enslin apparatus. Both force and water uptake data were collected by a computer and stored for subsequent analysis.

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Fitting of both water penetration and force development curves was performed with a commercially available software package for non-linear regression analysis.

This enables an examination of the relationships between force development and water penetration on the basis of homogeneous rate parameters.

The apparatus was validated on a model tablet formulation based on dicalcium phosphate dihydrate with carboxymethylstarch.

Besides application in fast disintegrating tablets, this approach could be useful to study the behaviour of swelling-controlled release systems, in which the release mechanism (swelling force) is triggered by water penetration.

INTRODUCTION

Ever since we started investigating tablet disintegration, our research has addressed the dynamic aspect of the process (1). A great deal of attention has been paid to force development inside disintegrating tablets and its relationships with disintegration properties (2,3).

Meanwhile, water uptake has been indicated by many authors as the major cause for disintegration mechanism activation (4,1) and as being related to disintegration properties (5,6).

In previous works, by our group, disintegrating force and classical water uptake measures were effected separately on the same tablet formulations, in order to achieve a general understanding of the disintegration phenomenon (7,8).

Disintegrating force was measured with an apparatus basically consisting of a stainless steel tablet holder and of a load cell (1). As the tablet was invaded by water, the force developing inside it was transmitted in the axial direction to the load cell, whose signal (duly amplified) was fed to a computer.

Since a tablet is invaded by water at its lower face and is prevented from expanding in the radial direction, the latter to avoid radial force losses and to ensure complete force transmission to the transducer, force measurement must be considered a uni-directional disintegration experiment (9).

In the same studies water uptake was measured using a modified Enslin apparatus (5) consisting of a glass tube connected with a water container placed on a microbalance. Water uptake was measured as the weight loss of the container .

Since the tablet is free to expand in all directions, water uptake measurement may be regarded as a three-dimensional disintegration experiment.
In the cited papers, the relationships between force development and water uptake were examined in series of different tablets. In order to modify formula hydrophilicity, the tablets were made of differing base materials and containing differing disintegrants in varying percentages.
It was observed that, on increasing tablet hydrophilicity (for instance on increasing disintegrant percentage), the total amount of water freely uptaken increased but it was not always parallelled by an increase in the total amount of force developed (7).
This could be attributable not only to the experimental conditions of the force measurements, which restrict the amount of water actually uptaken by the tablet, but also to the hydrophilic interactions between disintegrant particles, which could limit the expansion of the system and therefore force transmission (10).

Moreover, when the relationships between the kinetics of force development, the kinetics of water uptake and disintegration time were investigated, it was found that, in water-insoluble formulations, a relationship existed, on a log-log scale, between disintegration time and both force development rate and water uptake rate (8).

On the other hand, the lack of a correlation between disintegration time and force development rate in some water-soluble formulations was attributed to the fact that part of the force developed is lost due to the dissolution of the matrix (8).

These conclusions, based on the phenomenological and separate analysis of the two processes (water uptake and force development), prompted further investigations of the processes themselves. In order to achieve this, it was necessary to undertake the two measurements, water uptake and force, in the same experiment.

This paper describes the integration of a modified apparatus for force measurement with a modified Enslin apparatus (11).

The data concerning disintegrating force development and water uptake were simultaneously collected during the experiment and recorded in the mass storage memory of a personal computer for subsequent (off-line) analysis.
In this way, it was possible to compare the behaviour of the two phenomena on the basis of the best fit parameters obtained, using different mathematic models.

This allows the kinetic analysis and a comparative evaluation of the two processes. Particular attention has been paid to the initial stages of the processes, which are often decisive in the assessment of process kinetics (12).
In order to assess the reliability and the reproducibility of the measurements, the apparatus was validated on a model formulation (based on dicalcium phosphate dihydrate) capable of efficiently transforming water uptake into force (8).

EXPERIMENTAL

Description of the Experimental Apparatus.

To assemble the apparatus for simultaneous force and water uptake measurements, the following items are required:
- a load cell, connected with a recorder (optional) and interfaced with the computer;
- a microbalance, provided with a serial interface RS 232 C or another, appropriate interface;
- a personal computer (IBM AT) to control the whole measurement process.

The apparatus is depicted in Fig. 1. The tablet holder, similar in geometry to the one employed for force measurement (1), is made of plexiglas. Its lower face consists of a sintered glass filter (20 mm diameter, 3 mm thickness), that is firmly secured to allow reliable force measurements and of sufficiently high capillarity to enable the drawing of water, without limitations,inside the tablet. The tablet is placed on the sintered glass filter and the tablet holder is screwed on to the load cell. The support of the load cell, which is positioned horizontally, can be displaced upwards and downwards with a micrometric device.
To effect measurements, the assembled force apparatus is lowered until the lower face of the filter contacts a water-swollen sponge placed on a modified Enslin apparatus (5).

The sintered glass draws water inside the tablet and water uptake is measured as the weight loss of the container, which is placed on a microbalance.
As contact between the filter and the sponge is established, which is checked by means of an optical device, weighing data begin to appear on the balance visual display.

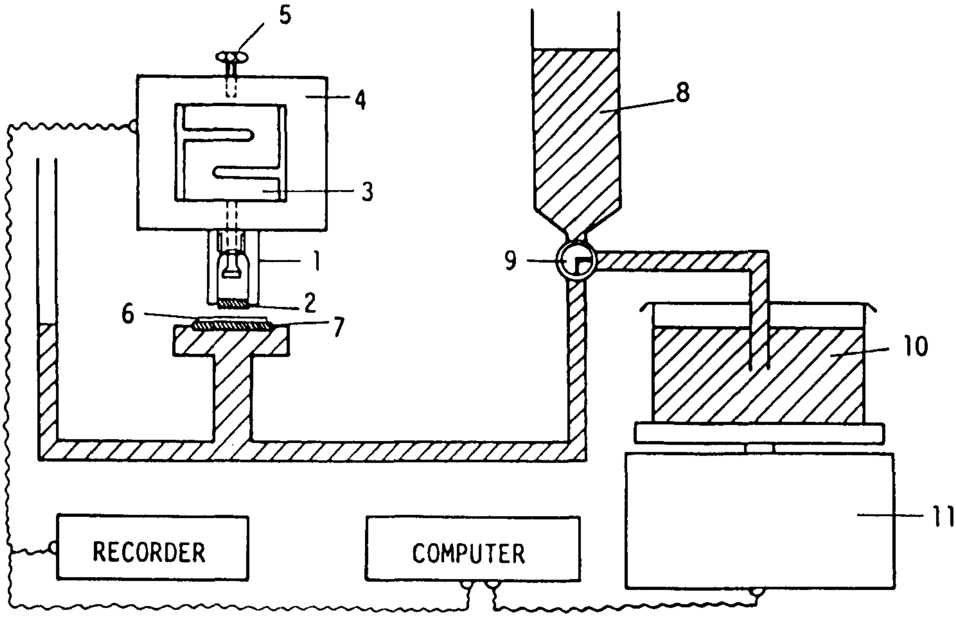

FIGURE 1

Design of the apparatus for simultaneous force and water uptake measurements.

1 - Tablet holder
2 - Sintered glass filter
3 - Load cell
4 - Support
5 - Micrometric device
6 - Sponge
7 - Glass filter
8 - Water reservoir
9 - Valve
10 - Container
11 - Microbalance

The force developed inside the tablet is simultaneously transmitted to the load cell, whose signal, duly amplified, is fed to a X-Y recorder, where the disintegrating force versus time curve is displayed.

Both load cell signals and weighing data are simultaneously collected, at suitable intervals (typical scanning time, 1-5 seconds), and stored, in files, in the memory of a personal computer for subsequent analysis.

Whereas force data need no further manipulations before analysis, water uptake data must be corrected for the amount of water uptaken by the filter.

To enable proper correction, repeated water uptake measurements are effected on the sintered glass alone, and the kinetics of the phenomenon is reconstructed and carefully taken into account in subsequent data fit computations.

A link program allows the import of both force data and water uptake data to a software package that is supported by the computer for subsequent fitting. The link program also envisages correction of data for those time lags that may be due to a delayed wetting of the sintered glass filter.

The available software provides for the fitting of curves to varying models, using a non-linear regression procedure and a library of equations (exponential, such as Weibull, simple hyperbolic, sigmoidal .....).

The goodness-of-fit is assessed both by estimating the standard deviation of the curve parameters and by analyzing the residual plots.

The comparison of water uptake and force development kinetics is based on the comparison of fitted curve parameters, which is effected by an appropriate statistical test (t test or a non parametric test).

Preparation of Tablets.

The materials used were:

- dicalcium phosphate dihydrate NF XVI (granulometric fraction 35-400 mesh) as base material
- crospovidone NF XVI (Polyplasdone ® XL, GAF; Milan; Italy) as disintegrant

A series of tablets, weighing 500 mg and containing 2% of talc and 5% of disintegrant were prepared by direct compression at 20°C and 50% R.H. (compression force level approximately 25.0 ± 0.5 kN).

RESULTS

Fig. 2 illustrates a typical profile for the water uptake of a sintered glass filter (0 porosity).

The phenomenon is fitted using a sigmoidal model (Siphar package, Simed, Créteil Cedex, France), according to the following equation:

$$Q = Q_{max} \frac{t^{\gamma}}{t_{50\%}^{\gamma} + t^{\gamma}}$$

where:

Q = amount of water uptaken at time t (mg); Q_{max} = total amount of water uptaken by the end of the experiment (mg); $t_{50\%}$ = half-time of water uptake (s); γ = slope factor (sigmoidicity).

The curve parameters (mean ± S.D. of ten replicates) are:

$Q_{max} = 282 \pm 10$; $t_{50\%} = 4.0 \pm 0.6$; $\gamma = 2.95 \pm 0.60$.

It may be noticed that the phenomenon is very rapid as indicated by the high γ value. Once the wetting process is activated, water uptake is completed in about 8 seconds.

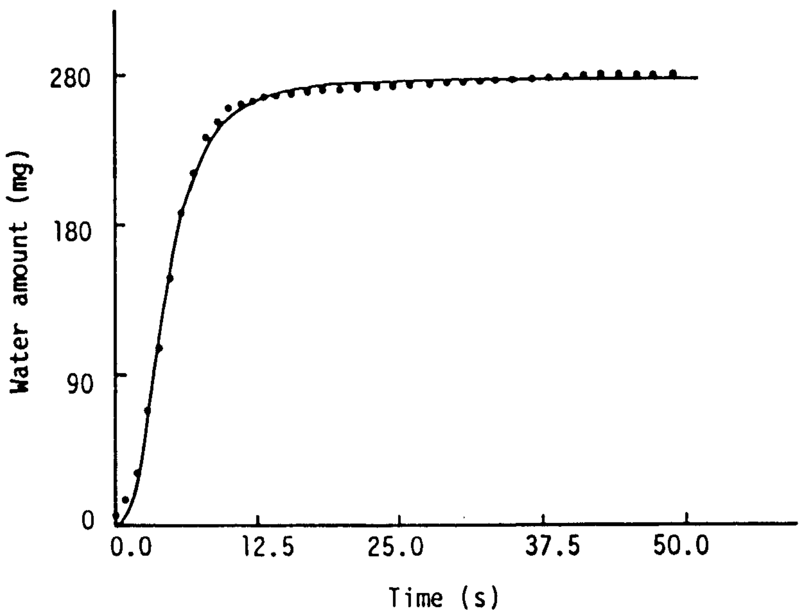

FIGURE 2

Typical water uptake profile of a sintered glass filter (0 porosity).

• experimental —— fitted

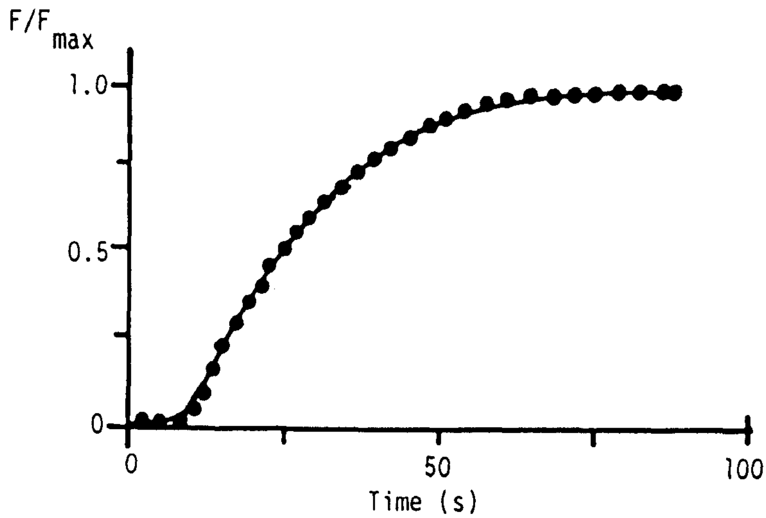

FIGURE 3

Normalized force (F/F_{max}) versus time profile for an individual Dicalcium Phosphate Dihydrate tablet.

• experimental —— fitted

F_{max} = 52.4 N; t_0 = 8.5 s; τ_d = 22.2 s; b = 1.18

Fig. 3 shows a typical profile of force developed versus time, relative to the model formulation examined. The curve was fitted using the well-known Weibull equation, as already described (3):

$$F = F_{max}\left(1 - e^{-\left(\frac{t - t_0}{\tau_d}\right)^b}\right)$$

where:

F = amount of force developed (N); F_{max} = maximum amount of force developed by the end of the experiment (N); t_0= time lag of the phenomenon (s); τ_d= time parameter (s); b = shape parameter.

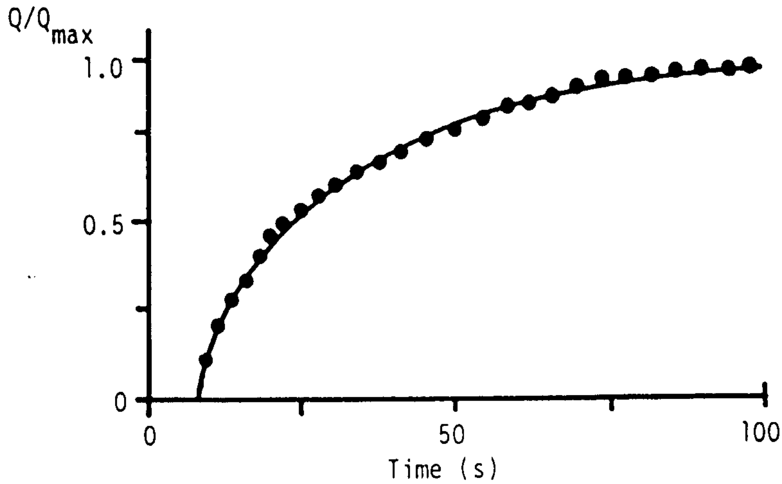

FIGURE 4

Normalized water amount (Q/Q_{max}) versus time profile for an individual Dicalcium Phosphate Dihydrate tablet.

• experimental —— fitted

Q_{max} = 103 mg; t_0 = 8 s; $t_{63.2}$ = 25.1 s; b = 0.81

The time lag is very reproducible and corresponds to the time needed to saturate the filter with water.

A typical profile of water uptake curve versus time for the model formulation is given in Fig. 4. The curve is obtained by subtracting from the experimental water uptake at a given time the amount of water uptaken by the filter, whose functionality in time is given by the sigmoidal equation mentioned above.

The water uptake curve is fitted, using the Weibull equation, to the following form (13):

$$Q = Q_{max}\left(1 - e^{-\left(\frac{t - t_0}{t_{63.2}}\right)^b}\right)$$

where:

Q = amount of water uptaken (mg); Q_{max} = total amount of water uptaken by the end of the experiment (mg); t_0 = time lag (s); $t_{63.2}$ = time needed to uptake 63.2% of the total amount of water (s); b = shape parameter.

It may be noticed that the time lag of water uptake is congruent with that of force development and equal to the time needed for filter saturation, confirming that, in the formulation tested, the two phenomena start simultaneously and that their delay is due to the presence of the sintered glass filter.

The two phenomena show comparable time parameter values, although their kinetics are not exactly the same as indicated by the different shape parameter values.

CONCLUSIONS

The described apparatus represents a reliable means to effect force development and water uptake measurements simultaneously in a reproducible way.

The computing facilities provided by user-friendly and flexible software enable off-line analysis of both water uptake and force development data. Modelling process kinetics facilitates the statistical comparison of fitted curves on the basis of homogeneous parameters, thus avoiding cumbersome computations. Experiments to date undertaken on the model formulation were exploited to validate the apparatus, but, of course, conclusions thus drawn on the relationship between force and water uptake cannot be extrapolated to other formulations.

In any case, the availability of fitted curve data in real time, thanks to the flexibility of the available software, makes further investigations on the same and/or other kinds of formulations relatively easy and rapid.

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