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EVALUATION OF FORMALIN-CASEIN AS A TABLET DISINTEGRANT

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ABSTRACT

Formalin-casein has been proposed as a tablet disintegrant under the trade name of Esma-spreng. The significance of water penetration on the disintegration mechanism has been evaluated by using different tablet constituents and by modifying the hydrophobicity inside the tablet. Formalin-casein appears to be a powerful disintegration agent when a sufficiently hydrophilic network has been created within the tablet. Swelling of the disintegrant has also been considered and evaluated under different conditions. However, this mechanism appears to be negligible in the disintegration process. In addition, a number of compressional characteristics were studied.

INTRODUCTION

In recent years, much attention has been paid to the bioavailability of drugs administered by conventional oral dosage forms. For tablets, the disintegration process ofen becomes a limiting factor for drug dissolution, especially for drugs with low solubility in water or in biological fluids. Factors that influence disintegration are numerous. Formulation-related factors, such as nature of diluents, binders, lubricants and, of course, disintegrants, are as important as manufacture-related factors, such as existence of a granulation stage during manufacturing, compressional levels and storage. To ensure correct tablet disintegration, it is necessary to understand the disintegrant properties, hence the disintegration mechanism.

Different theories (1, 2) concerning disintegrant action mechanisms have been proposed in the past. For insoluble products, they include the swelling of disintegrant particles (3, 10, 11), modification of particle particle interactions (6-9), porosity and capillary action (9), release of compressionally-induced deformations due to liquid contact (2) and air dilation (14). These theories are not necessarily contradictory, although the two first are highly probable in many cases.

Whatever the mechanism, and prior to disintegration, penetration of the liquid medium inside the tablet is necessary (12, 13). This phenomenon is influenced by the nature of the porous network (8) developed within the tablet during compression (nature and size of the pores, wettability of the walls of the porous network by liquids) and by the properties of the liquid medium (surface tension, viscosity, polarity). When the liquid has penetrated into the tablet, the action mechanism of the disintegrant takes place, so that disintegration occurrs.

Formalin-casein is an insoluble semi-synthetic polymer derived from casein and is used as a tablet disintegrant (15,16). As it is a hydrophilic substance completly digestible (17), it minimizes possible biopharmaceutical problems due to drug adsorption effects. The aim of this study is to investigate the disintegration mechanism of this product.

MATERIALS AND METHODS

The disintegrant used was the commercial grade of formalin-casein (Esma-spreng fine, SAPA, Ezanville, France). Model substances were acetylsalicylic acid (ASA, Prolabo, Paris, France) and dicalcium phosphate dihydrate (Emcompress, Ed. Mendell, Carmel, N.Y., U.S.A.). The charateristics of these products, including true, bulk, tapped densities, Carr's compressibility index (18), loss on drying and particle size (as estimated by sieve and Coulter counter measurements) are presented in Table 1. Magnesium stearate (Prolabo, Paris, France) was used as a lubricant. All other reagents were analytical grade.

The model substance was placed in a 1 liter container, which was about one-third full, and then mixed with varying quantities of disintegrant in a mixer (Turbula, Model T2G, Bachhofen, Basle, Switzerland) at 70 r/min. for 10 minutes.

TABLE 1
Physical characteristics of raw products

Substance	True density ($g.cm^{-3}$)	Loose bulk density ($g.cm^{-3}$)	Tapped bulk density ($g.cm^{-3}$)	Carr's index (%)	Loss on drying (%)	Particle size (μm)
Dicalcium phosphate	2,873	0,855	0,990	13,6	6,7	125
Acetylsalicylic acid	1,362	0,662	0,735	9,9	1,7	423
Formalin casein	1,195	0,172	0,222	22.5	9,7	10

Compression was carried out at different pressure levels by using an instrumented single-punch tabletting machine (KORSH EK-0, Berlin, F.R.G.) employing flat punches of 12 mm in diameter. In order to obtain reproducible results, compression was always performed on the same true volumetric quantity of powder (19), corresponding to tablets of 12 mm in diameter (D) and 2 mm in height (h) at zero porosity. The powder weight, M, corresponding to such tablets was calculated by using the powder true density (ρv), according to the following equation:

$$M = \frac{\pi D^2 h}{4} \cdot \rho v \quad (1)$$

Tablets were used after at least two days in order to allow any possible modification after compression and stored in glass containers under plastic caps.

Tablet weight variations were determined on 10 tablets. Tablet porosity was determined by measuring the diameter and the thickness of 10 tablets, considering the true density of the initial components. Fracture strength of the tablets was also measured with a hardness tester (Schleuniger model 2E, K. Schleuniger, Zürich, Switzerland) and expressed as tensile strength (20).

In addition, compressional properties of the different powder blends were characterized by using the RYSCHKEWITCH

TABLE 2
Ryschkewitch Equation Parameters, Corresponding to Diclcium Phosphate Tablets Lubricated with 0.5% Magnesium Stearate and Containing Varying Percentages of Formalin-casein as Disintegrant.

Formalin-casein (%)	b	Lnσxmax	r^2
0	-0.1668	5.895	0.998
1	-0.1755	6.375	0.996
1.5	-0.1757	6.347	0.998
2	-0.1760	6.302	0.992
3	-0.1528	5.638	0.982

equation (21) which expresses the relationship between fracture strength, σx , and ε the remaining porosity in the tablet:

$$\sigma x = \sigma x\ max . e^{-b\varepsilon}$$

where $\sigma x max$ represents the maximal attainable fracture strength for $\varepsilon = 0$ and where b is a constant.

Measurement of disintegration time was carried out by using the European Pharmacopeia apparatus (Erweka ZT6, Heusenstamm, F.R.G.), equipped with an electronic sensor system. Each result is the mean of six determinations. All the tests were performed at 37°C either in deionized water (pH ◘ 5.9) or in other media.

Disintegrant swelling degrees in the different disintegrating media were determined by using a Coulter counter (Coultronics, Margency, France). For each disintegrant

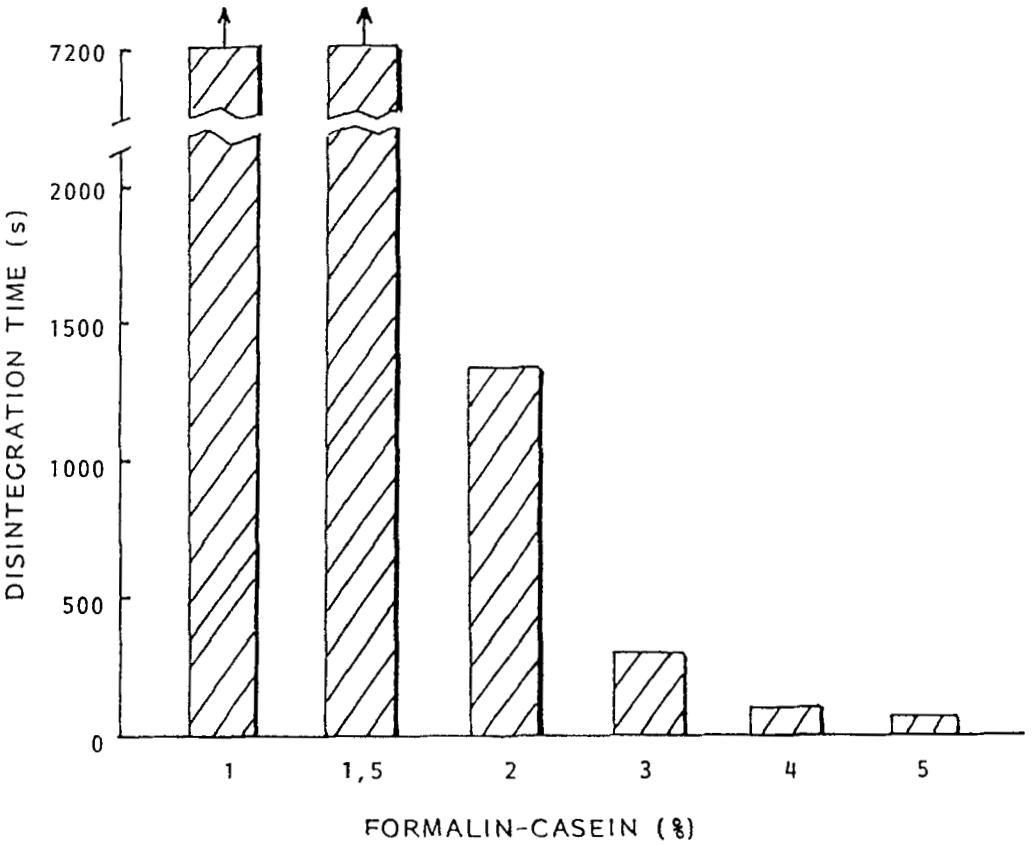

FIGURE 1

Influence of formalin-casein content on disintegration time of acetylsalicylic acid tablets prepared at constant porosity (about 3%). Arrow indicates a disintegration time greater than 12 hours

medium to be tested, the particle size distribution of formalin-casein was measured after dispersion of a weighted powder quantity under agitation into the media for 15 minutes, and then, expressed as a volume distribution. Thus, it was possible to calculate the whole volume of a disintegrant sample immersed in a given medium. Relative swelling degrees, expressed in percent, were obtained by comparing the measured volume to the volume obtained for the disintegrant immersed in Isoton.

RESULTS AND DISCUSSION

From the physical characteristics of the starting materials summarized in Table 1, it is possible to observe that dicalcium phosphate and acetylsalicylic acid exhibit lower compressibility indexes than formalin-casein, which appeared to be more compressible. The naturally hydrophilic nature of formalin-casein, demonstrated by the significant water content, is also important.

Compressional Properties and Mechanical Strength

Small percentages of formalin-casein in direct compression formulae do not significantly affect the mechanical strength of tablets, as shown by examination of the parameters of the RYSCHKEWITCH equation parameters (Table 2). An examination of the data corresponding to dicalcium phosphate tablets, lubricated with 0.5% magnesium stearate, shows that addition of slight quantities of formalin-casein (0 to 5%) do not modify tablets mechanical properties.

Influence of Formalin-casein Content in Tablets

Table 3 shows disintegration times in water of dicalcium phosphate tablets, lubricated with 0.5% of magnesium stearate, and containing increasing percentages of formalin-casein. As previously reported (12), it must be pointed out that dicalcium phosphate tablets do not undergo any disintegration if there is no disintegrant, whatever the compressional pressure. Thus, dicalcium phosphate can be used as a model substance in order to appreciate the power of a given disintegrant. Addition of more than 1% of formalin-casein to dicalcium phosphate tablets, prepared at a constant pressure of almost 270 MPa, which corresponds to a porosity of about 37%, leads to very short disintegration times, less than one minute. An interesting feature is that the addition of more than 1% formalin-casein leads to a disintegration process which is independent of compressional pressure. This is not the case when only 1% formalin-casein is employed.

In order to determine the effect of increasing disintegrant levels in more hydrophobic tablets, acetylsalicylic acid was chosen as another model substance. Figure 1 shows the influence of formalin-casein content upon disintegration time for non-lubricated acetylsalicylic acid tablets prepared at a constant porosity of about 3%, which corresponds to a pressure of about 260 MPa. As for dicalcium phosphate, disintegration occurs only when a sufficient

TABLE 3
Disintegration Times (s) of Dicalcium Phosphate Tablets (Mean of Six Determinations), Lubricated with 0,5% of Magnesium Stearate, and Containing Increasing Formalin-casein Percentages as a Disintegrant.

Pressure (MPa)	Formalin-casein				
	0%	1%	1.5%	2%	3%
55	7200	164	56	41	31
108	7200	171	45	35	29
161	7200	473	46	37	28
215	7200	1155	54	42	29
264	7200	2994	63	42	30

percentage of formalin-casein is added. In this case, the addition of 2% formalin-casein is necessary to observe tablet disintegration. However, more than 3% formalin-casein is necessary in order to obtain a disintegration time of less than one minute.

Continuous Network Hypothesis Examination

Examination of the transition between non-disintegrating behavior and disintegrating behaviour, as reported in Table 3 for dicalcium phosphate tablets, is interesting. The addition of 1% formalin-casein gives a very pronounced pressure dependence of the disintegration time. This phenomenon completly disappears when 1.5% formalin-casein is added. When disintegration time is plotted against tablet porosity for the same formalin-casein concentrations (Figure 2), similar features are encountered. Consequently, differences between porosities into the tablets cannot be invoked in order to explain the differences observed.

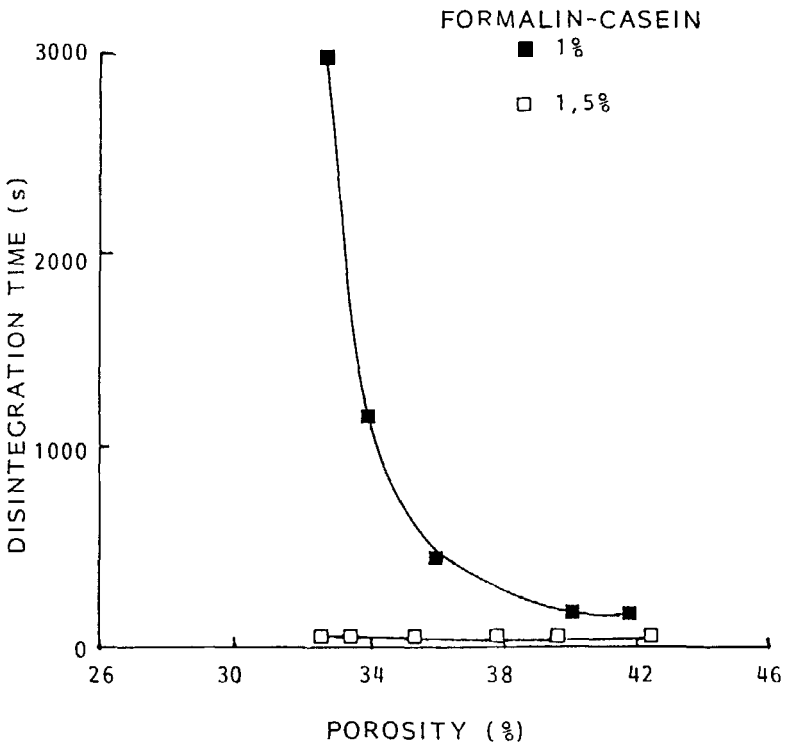

FIGURE 2

Relationship between porosity and disintegration time of dicalcium phosphate tablets, lubricated with 0.5% magnesium stearate, containing 1.0% and 1.5% formalin-casein disintegrant

It has been reported (6,7,8,9) that it was necessary to establish a sufficiently continuous hydrophilic network around the other particles (diluent or active drug) in order to observe tablet disintegration. In the case of dicalcium phosphate tablets, it is likely that 1% formalin-casein is not sufficient to establish a continuous hydrophilic polymeric network, but that 1.5% is satisfactory. Supporting this hypothesis is the sharpness of the transition. Such a phenomenon has been reported previously for acetylsalicylic tablets containing increasing quantities of starch by RINGARD et al. (6). When a sufficient hydrophilic network is established, disintegration time becomes independent of tablet

porosity. Examination of Table 3 confirms this hypothesis. It shows that the disintegration time of dicalcium phosphate tablets, prepared at about 270 MPa (exhibiting an almost constant porosity of about 37%) and lubricated with 0.5% magnesium stearate, drops suddenly when the percentage of formalin-casein is higher than 1,0%.

Based on sphere coordination indices calculations, a methodology for the calculation of the theoretical disintegrant quantity, Q, which is necessary to develop a continuous disintegrant network (made of a simple layer of disintegrant particles) in a tablet has been proposed by RINGARD and GUYOT-HERMANN (7), where D1 and D2 are respectively the particle sizes of the disintegrating agent and of the diluent, and where d1 and d2 are the corresponding true densities:

$$Q = 0.32 \cdot \frac{d1}{d2} \cdot \left[\left(\frac{D1}{D2} + 1 \right)^3 - 1 \right] \quad (3)$$

However, the disintegrant quantities calculated by this method are indicative only, since generally they do not fit exactly to disintegration data. By using true densities and the particle mean diameters of table 1, the percentage necessary to obtain full coverage of dicalcium phosphate particles by formalin-casein particles would be about 3.5%. This value is higher than the threshold value for disintegration of 1.5% observed in Table 1. In the case of acetylsalicylic acid, the calculated value is 2.0% and have to be compared with the threshold value of 3.0% for disintegration time (Figure 3). These slight discrepancies may be due to many factors neglected during the calculation, such as particle fragmentation during compression, irregular shape of particles and particle swelling. Although the values observed during disintegration experiments do not fit exactly to the calculated values, they have the same magnitude, supporting the hypothesis of the continuous network.

Influence of the Hydrophilic/Hydrophobic Balance

For disintegration to occur, it is necessary to have a sufficiently hydrophilic network in the tablet in order to have a rapid water uptake, leading to the rupture of interparticulate bonds (6-9). Liquid medium penetration through the tablet depends on the hydrophilic/hydrophobic balance that is established in the tablet. As previously pointed out, although some water uptake may occur in pure

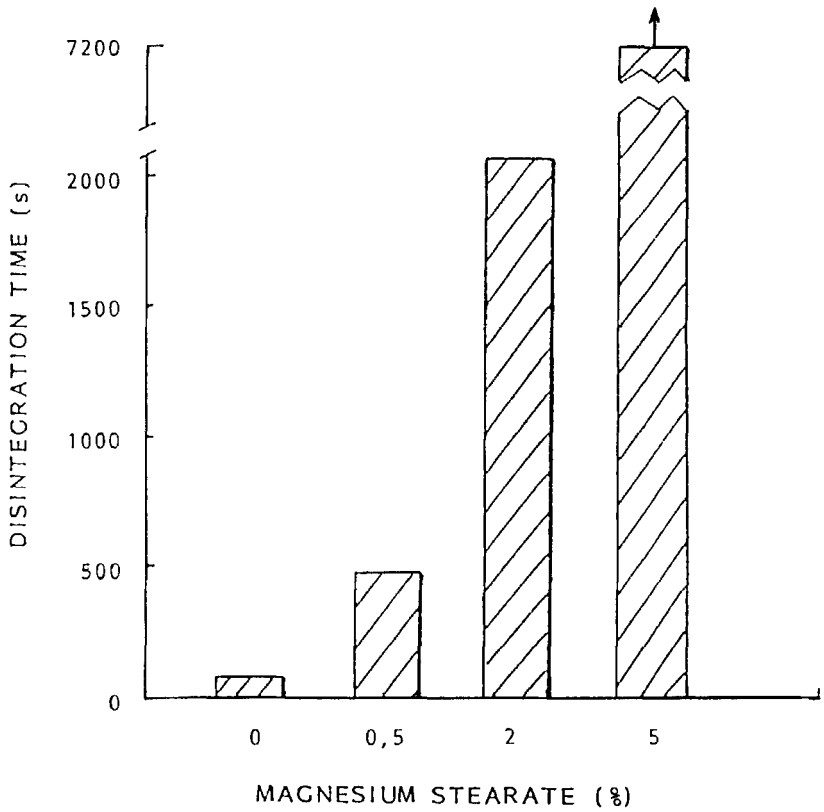

FIGURE 3

Influence of magnesium stearate content on disintegration time of diclcium phosphate tablets prepared at constant porosity (about 37%), lubricated with 0.5% magnesium stearate and containing 1.0% formalin-casein. Arrow indicates a disintegration time greater than 12 hours

dicalcium phosphate tablets (22), Table 3 shows that water is unable to dissociate dicalcium phosphate particles. Furthermore, lubrication by hydrophobic lubricants such as magnesium stearate increases the hydrophoby of the tablets.

Figure 3 demonstrates the incidence of the hydrophylic/hydrophobic balance in the tablet upon disintegration. Dicalcium phosphate tablets prepared at constant porosity (about 37%) with 1% formalin-casein and

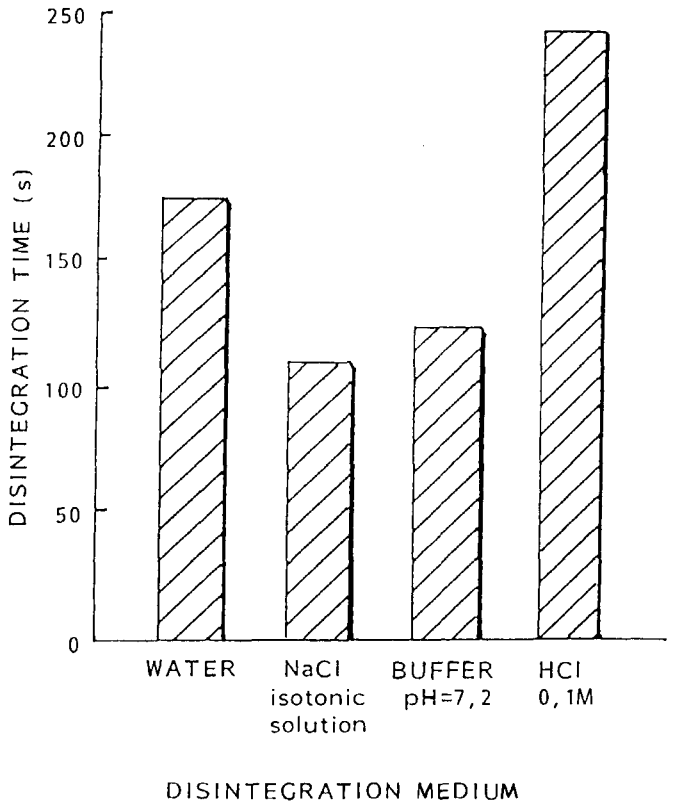

FIGURE 4

Effect of disintegration medium composition on disintegration time of dicalcium phosphate tablets prepared at constant porosity (about 32%), lubricated with 0.5% magnesium stearate and containing 2.0% formalin-casein

containing increasing quantities of magnesium stearate exhibit increasing disintegration times. Due to its hydrophobic nature, the addition of magnesium stearate progressively inhibits water uptake into the porous network so that disintegration becomes almost impossible when the stearate content reaches 5%.

Influence of the Composition of the Disintegration Medium

Figure 4 shows the effect of the composition of some commonly used disintegration media on the disintegration time

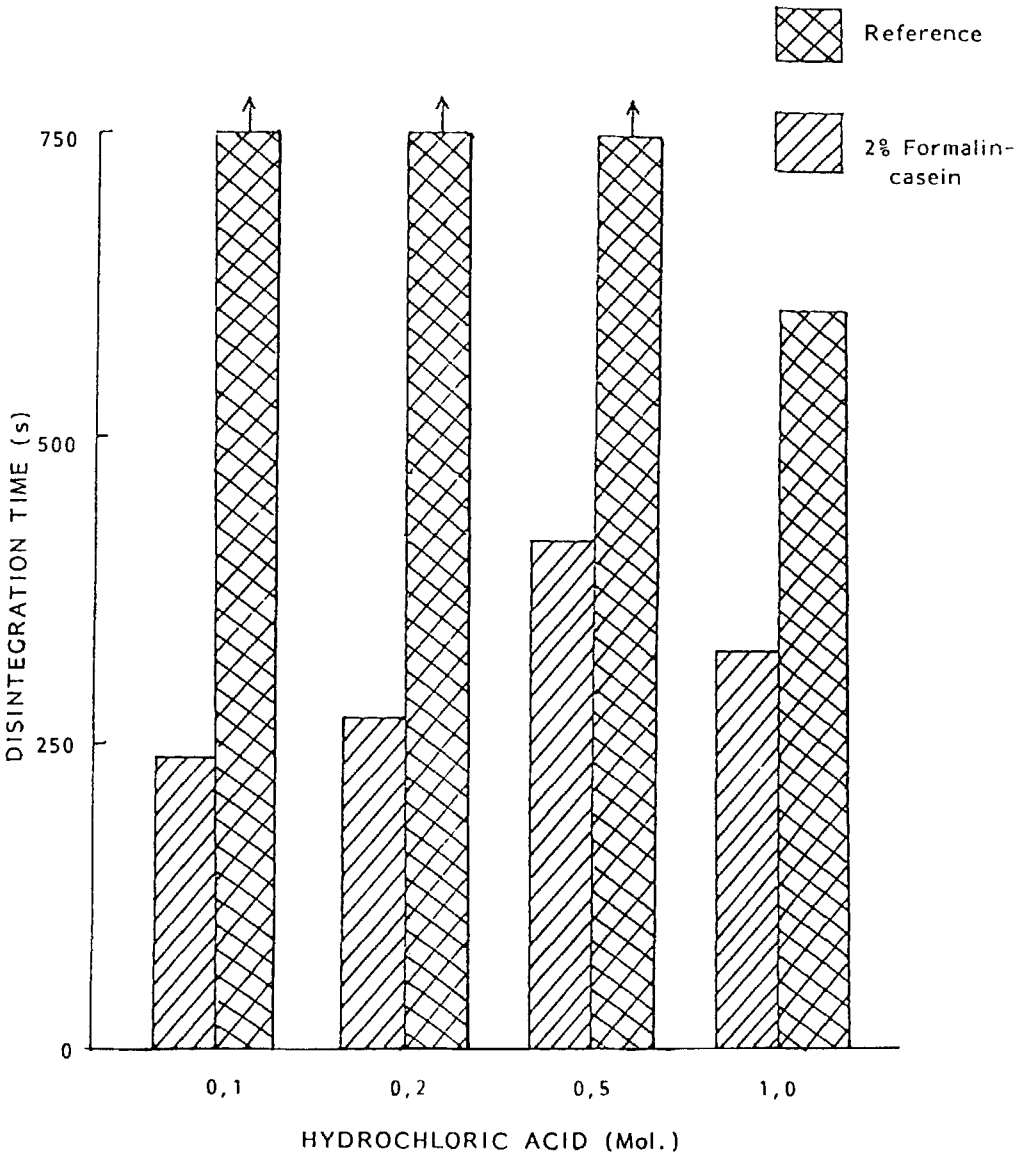

FIGURE 5

Influence of disintegration medium hydrochloric acid content on disintegration time of dicalcium phosphate tablets prepared at constant porosity (about 32%), lubricated with 0.5% magnesium stearate and containing 2.0% formalin-casein. Reference is made to dicalcium phosphate tablets lubricated with 0.5% magnesium stearate prepared under the same conditions. Arrow indicates a disintegration time greater than 120 minutes

TABLE 4
Relationship between Disintegration Time in Various Media (Expressed as Relative Values Compared with Disintegration Values in Isoton) and Swelling Behaviour of Formalin-casein in the same Media, for Dicalcium Phopsphate Tablets Lubricated with 0.5% Magnesium Stearate and Containing 2% Formalin-casein and Prepared at 270 MPa.

Medium	Relative disintegration times (%)	Swelling (%)
Water	+55.4	---
Isoton	0	---
pH 7.2 buffer	+7.1	---
HCl 0.1 M	+115.2	+10.3
HCl 0.2 M	+138.4	+8.7
HCl 0.5 M	+275.9	+16.2
HCl 1.0 M	+192.9	+4.2

of dicalcium phosphate tablets, prepared at a constant porosity of about 32% (corresponding to a pressure of about 270 MPa), containing 2.0% formalin-casein. Fluctuations in disintegration time are quite pronounced since tablets disintegrate almost twice fast in an isotonic sodium chloride solution than in a 0.1 M hydrochloric solution.

Figure 5 shows the effect of the hydrochloric acid concentration of the testing medium for the same tablets as previously, compared with tablet behaviour without formalin-casein. Increase in the acidic content up to 0.5 Mole/l slows down the disintegration time whithout provoking any disintegration of the reference tablets. For one mol/l hydrochloric acid, disintegration of the pure dicalcium phosphate tablets occurs, due to its solubility in strong acidic solution. This fact can explain the slight decrease in the disintegration time of the tablets containing formalin-casein.

Swelling Behaviour of Formalin-casein Particles

A number of authors have shown the existence of correlations between the swelling behaviour of various disintegrants and their performances in tablet disintegration for a given medium (4,5). Figures 4 and 5 present results corresponding to dicalcium phosphate tablets containing 2% formalin-casein. It has been shown previously that this quantity was almost sufficient to ensure the establishment of a hydrophilic network all round the diluent or active drug particles. The different disintegration times encountered in Figures 4 and 5 can be related either to formalin-casein properties, such as swelling behaviour, or to modifications of solid liquid interactions.

However, the hypothesis of a modification in the swelling behaviour of formalin-casein is not very satisfactory. Table 4 presents the comparative values of swelling of formalin-casein (values related to isoton measurements). In the case of an increase in the acidic content of the disintegration medium, swelling is hardly modified in comparison with the relative increase in disintegration times. Thus, particle swelling cannot be invoked in order to explain variations in the disintegration time related to changes in the disintegration media. Modifications of interparticulate forces have been stressed by GUYOT-HERMANN et al. (9). In the present case, modifications of solid liquid interactions, related to variations in the liquid properties, can lead in turn to modifications of the interparticulate forces. Such phenomena may be involved in the present disintegration process.

Conclusion

Formalin-casein properties have been studied paying particular attention to the disintegration mechanism of this polymer. Modifications of disintegration time when polymer quantity is varied, and also when variations in the degree of tablet hydrophoby are induced, support the hypothesis of the continuous hydrophilic network. Tablet disintegration is efficient when the amount of formalin-casein added, which depends on powder respective particle sizes, is sufficient to develop a polymeric particle network around the other particles. On the other hand, formalin-casein particle swelling is not involved in the intimate mechanism of tablet disintegration, and cannot explain variations in the disintegration time when the disintegration medium composition is varied.

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