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THE INFLUENCE OF THE SWELLING CHARACTERISTICS OF STARCH AND STARCH DERIVATES ON THE DISINTEGRATION OF POWDERS, PACKED IN HARD GELATIN CAPSULES.

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Starch and starch derivates are frequently used in tablets to improve the disintegration. Their disintegrating action has mainly been attributed to the swelling of the particles when they are immersed in an aqueous solution. It has been assumed that tablet disintegration would be related to the ratio between the pore diameter and the linear growth of the disintegrant particles. The present work investigates the relationship between disintegrant swelling, pore diameter and drug release rate for loosely packed powderbeds in hard gelatin capsules.

INTRODUCTION

The release of drugs, and especially of hydrofobic drugs, from hard gelatin capsules is often seriously limited by the disintegration rate of the powdercylinder in the capsule. A possible remedy for this problem can be found in the use of disintegrants. These adjuvants have been widely used in tablets to promote the disintegration of these highly compressed pharmaceutical dosage forms. The mechanism of action of disintegrants in tablets has been attributed mainly to the swelling of the particles when they are brought into contact with water. According to Couvreur[1], a disintegrant should be effective if the linear growth of the disintegrant particles during swelling is greater than the mean pore

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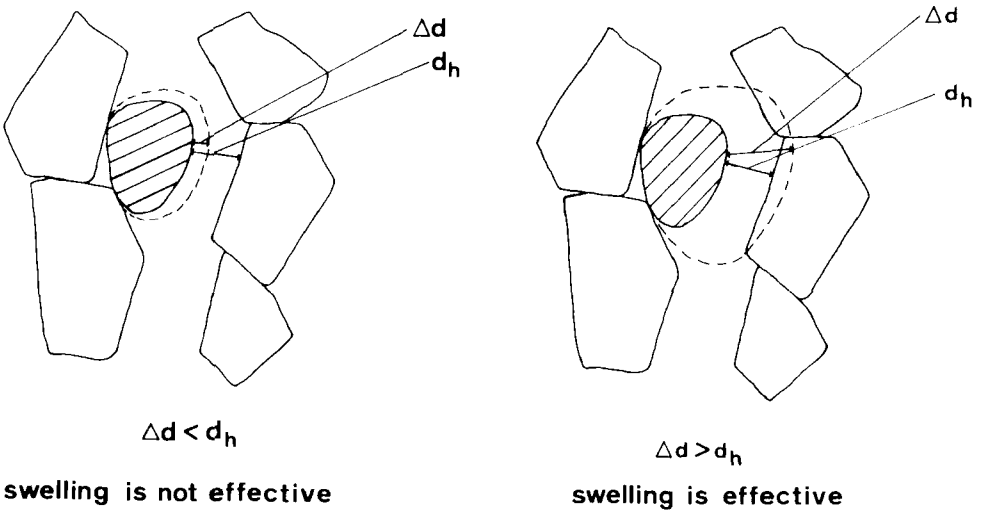

FIGURE 1

Theoretical representation of the influence of swelling of disintegrant particles on the disintegration of the powderbed.

diameter in the powderbed (Fig. 1). Compared to tablets however, the powder in capsules is much more porous and less compressed.

The present work investigates the relationship between disintegrant swelling, porosity and pore diameter of the powdercylinder and release rate of the drug from gelatin capsules.

MATERIALS

In these experiments, phenacetin powder (Bayer ,Leverkusen, W-Germany) was used as a model drug. Potato starch and sodium starch glycolate (Explotab^{R}, Roquette freres, Lille, France) were the selected disintegrants. These two materials exhibit greatly different swelling characteristics. Lactose 200 mesh (D.M.V., Veghel, Holland) was used as a non swelling hydrophylic reference substance. By means of an air-jet sieve (model A200LS, Alpine AG Maschinenfabrik, Augsburg, W-Germany) the disintegrants were divided in a fine fraction, with particles smaller than 45 μm, and a coarse fraction, with a particle size between 45 and 80 μm.

METHODS

Determination of Particle Size and Swelling of the Adjuvants

The diameters of the 'dry' particles are measured on a suspension in paraffin oil. The diameters of the swollen particles are determined on a suspension in simulated gastric fluid. Microphotographs of the suspensions are brought on the digitizer pad of a Kontron MOP-AMO2 apparatus. After manual tracing of an individual particle, the apparatus calculates the projected area and transmits this value to a HP 9815A calculator, which determines the size distribution and its specific parameters.

Preparation of Powder Mixtures and Filling of the Capsules

A Turbula mixer (Willy Bachofen Maschinenfabrik, Basel, Switzerland) was used to prepare mixtures of phenacetin with 50% of the adjuvants. Different quantities of these powder mixtures were compressed to a constant volume in gelatin capsules. Thus powder-cylinders were obtained with varying porosities, and as a consequence with different pore diameters. The capsules were filled by means of a special filling apparatus, which allows to compress the powders to a constant volume. The applied force is measured by means of a piezo-electric force transducer, and after amplification the signal is recorded on a fast ballistic recorder. Two different dies can be used in this press: The first one is used to fill an empty capsule-body with the powder mixture. The second one is a measuring-die. It permits to compress the powder to a cylinder which has the same diameter and volume as the powder cylinder in a capsule.

Determination of the Pore Diameter

The mean hydraulic pore diameter in the powdercylinders is measured by means of an adapted Blaine apparatus [3-5]. The powders are compressed into the measuring die and placed onto the Blaine apparatus, and the time, needed by a constant volume of air to flow through the powder is measured.

Drug Release Rate

The drug release rate is measured with an automated beaker method. The results are expressed as dissolution-efficiency [6] (D.E.).

RESULTS

Swelling Efficiency of the Disintegrants

The results of the particle size measurements in aqueous and non aquous media are given in table 1. Both powder fractions of starch glycolate show a dramatic diameter increase in water of more than 300%. This phenomenon however seems to be very pH dependant. Indeed, the swelling is much less pronounced in simulated gastric fluid (S.G.F.), which has a pH of 1. Still, even in these circumstances, the increase of diameter of the Explotab^{R} particles compares very favorably with that of the native potato starch. Swelling of potato starch is not very dependent on the pH of the solution. In either medium the diameter increases with about 11 to 14%.

Influence of Disintegrant Type on Drug Release

Figure 2 shows the drug release rates from hard gelatin capsules as a function of porosity, for mixtures of phenacetin with lactose and with the fine powder fractions of potato starch and sodium starch glycolate. As can be seen in table 1, these 3 types of adjuvants have comparable particle sizes.

-Potato starch < 45um is not a very good disintegrant in capsules. In powderbeds with a high porosity (40% or more) it does not perform better than lactose. At lower porosities (higher compression forces) its efficiency improves slightly, but still remains relatively low. At neither porosity level the powdercylinders were completely disintegrated within 2 hours.

-Starch glycolate < 45um, which has a higher swelling capacity than potato starch < 45 um, is a much better disintegrant in gelatin capsules. Porosity variations have hardly any influence on its activity. For these mixtures all of the powdercylinders disintegrate within less than 10 minutes.

TABLE 1

Particle Size and Swelling

	PARAFFIN	WATER		S.G.F.	
	diam.	diam.	growth	diam.	growth
	d1 (μm)	d2 (μm)	Δd=d2-d1 (μm)	d3 (μm)	Δd=d3-d1 (μm)
potato starch <45μm	33.79	37.64	3.85	38.74	4.95
" " 45-80μm	61.34	69.91	8.57	70.32	8.98
starch glycolate <45μm	34.90	139.39	104.49	52.24	17.34
" " 45-80μm	62.45	233.56	171.11	81.97	19.52
lactose 200 mesh	22.40	-	0	-	0
phenacetin	43.90	-	0	-	0

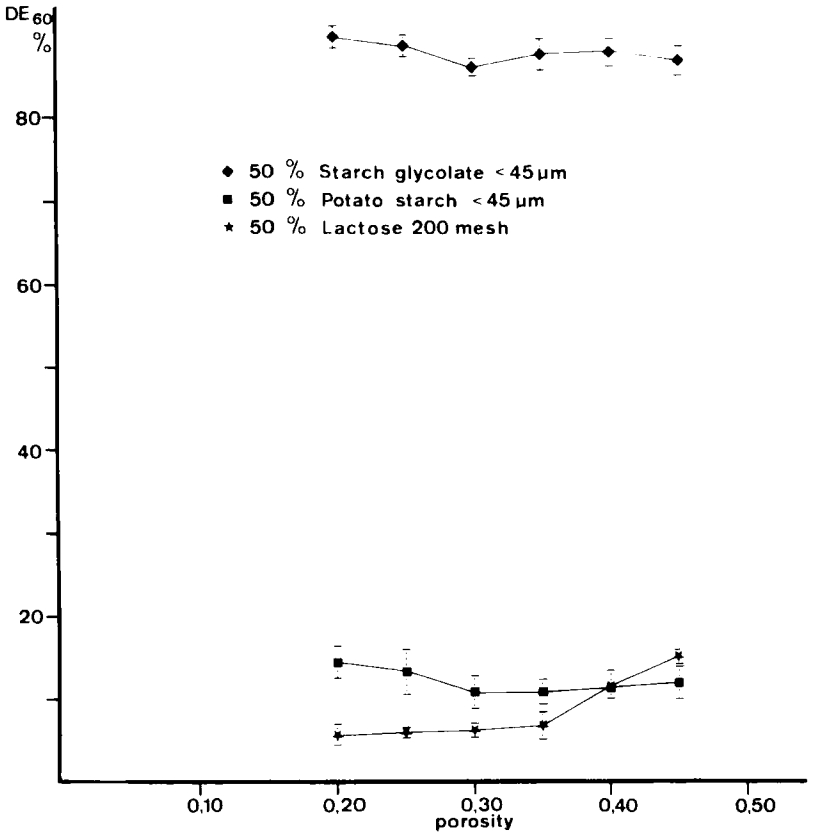

FIGURE 2

Drug release rate of mixtures of phenacetin with different types of adjuvants of comparable particle size, as a function of porosity.

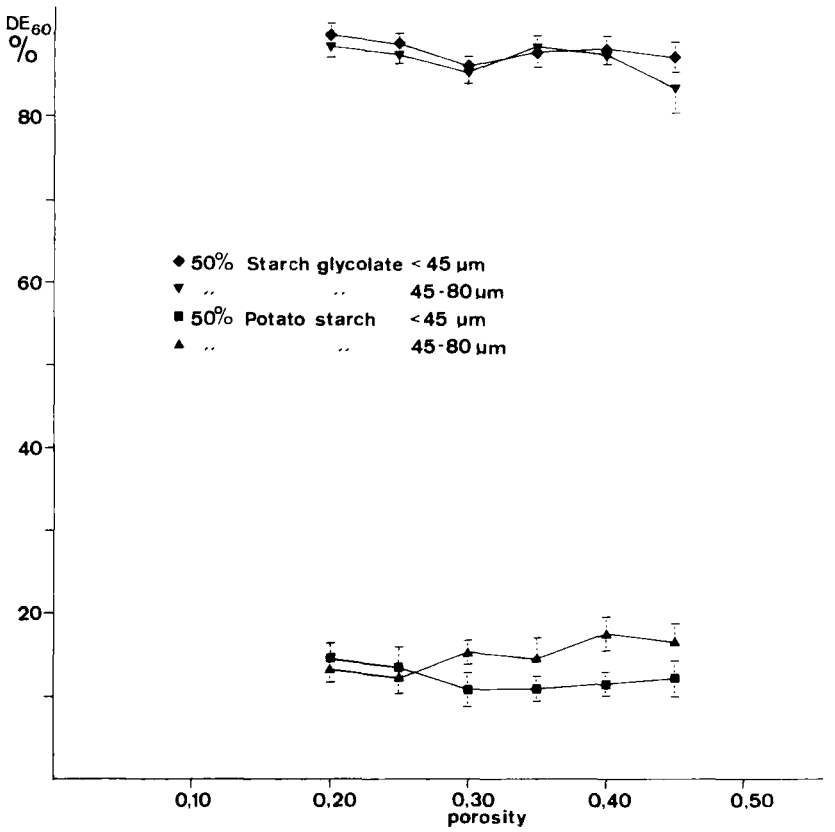

FIGURE 3

Drug release rate of mixtures of phenacetin with disintegrants of different particle size, as a function of porosity.

Influence of particle size on drug release

The drug release rates from hard gelatin capsules is shown in figure 3 as a function of porosity, for mixtures of phenacetin with different particle size fractions of potato starch and of sodium starch glycolate. Figures 4 and 5 give the mean pore diameter of the powder cylinders as a function of porosity, for starch glycolate and potato starch respectively. They also represent the mean increase in diameter of the disintegrant particles as a result of swelling.

For starch glycolate there is no significant difference in release rate between the two sieve fractions. Both perform very

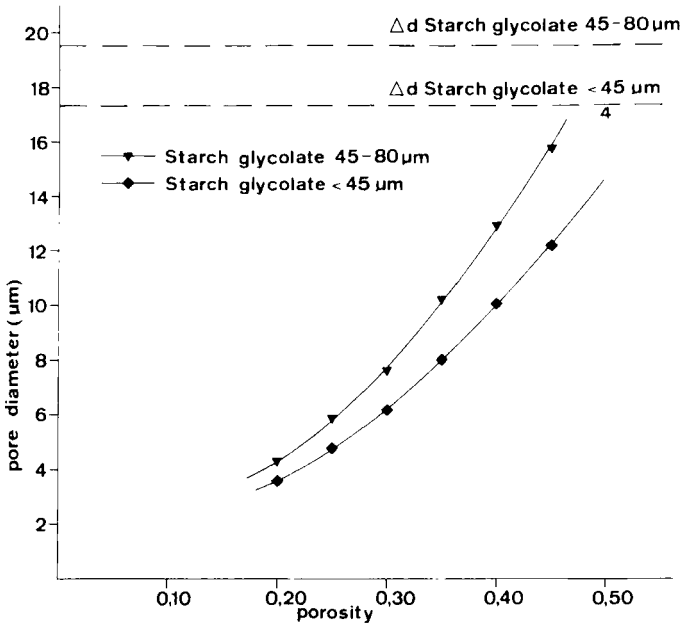

FIGURE 4

Mean pore diameter of mixtures with starch glycolate, as a function of porosity (——), compared with the diameter increase of the disintegrant particles (----).

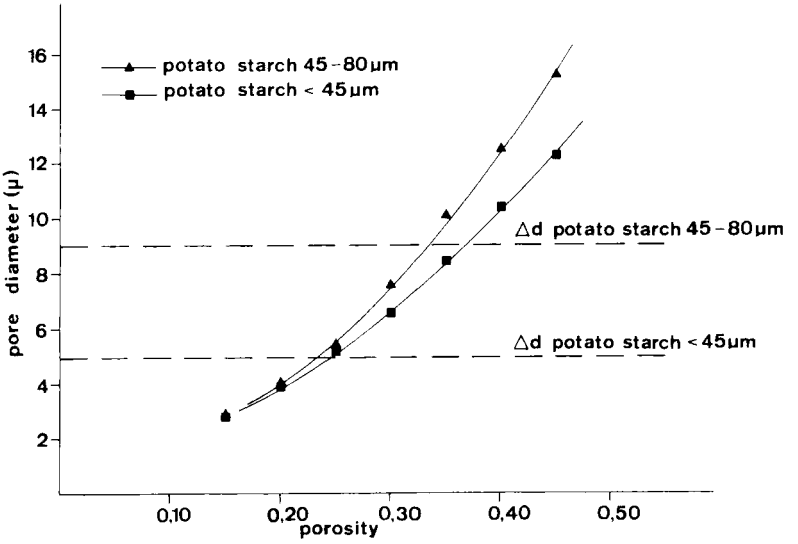

FIGURE 5

Mean pore diameter of mixtures with potato starch, as a function of porosity (——), compared with the diameter increase of the disintegrant particles (----).

well at all porosity levels. Disintegration is very fast in all cases. This is in agreement with Couvreur's theory, since fig. 4 clearly shows that for both fractions the linear growth of the particles is greater than the mean pore diameter, for all porosities tested.

For mixtures with potato starch fig. 5 clearly shows that at porosities of less than 0.25 and 0.35 respectively, the linear particle growth of the fractions < 45um and 45-80um is greater than the mean pore diameter. This suggests a rapid disintegration and a high release rate. In reality none of the powderbeds disintegrates within 120 minutes. Variations in porosity do not produce great changes in release rate, as shown in figure 3. In fact, a marked swelling of the powdercylinders can be observed after rupture of the gelatin wall. It is more pronounced in the powderbeds with low porosity. This swelling however does not result in disintegration of the powderbed.

CONCLUSIONS

From the results obtained, following conclusions may be drawn:

- Potato starch is not a good disintegrant in gelatin capsules.
- The stronger swelling starch glycolate is a much better disintegrant in capsules.
- At the used concentration, porosity variations do not have a great influence on disintegration time and release rate.
- Swelling of the disintegrant particles seems to be a very important factor. However, the theory which relates disintegration time to the relation of linear particle growth and mean pore diameter does not seem to hold in the case of hard gelatin capsules.

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