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DISINTEGRANTS IN SOLID DOSAGE FORMS

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SUMMARY

The dynamic approach to tablet disintegration, which is based on the measurement of the force that develops inside the compact upon water entrance, is basically taken up.

The combined measurements of force development and water uptake, simultaneously effected on the same compact, provide a novel parameter that is proposed to quantify and compare the efficiency of disintegrants.

The new parameter, which is based on the "force-equivalent" concept, expresses the capability of a disintegrant of transforming water uptaken into swelling (or disintegrating) force. A few examples, that illustrate the usefulness of this parameter for disintegrant characterization, are given.

In parallel to the quantification of swelling (or disintegrating) efficiency inside compacts, attention is also being paid to the characterization of swelling disintegrants as pure materials.

In particular the case of the so-called limited swelling materials, for which the quantification of intrinsic swelling (particle volume increase in swelling media) is critical, is considered.

The applicability of an instrumental method, which is based on the employment of a Coulter Counter, is discussed alternatively to microscopic methods.

Disintegrant characterization may also be considered in view of new possible exploitations of the swelling properties of polymers in controlling drug release.

INTRODUCTION

Dealing with such a classical item as solid dosage form disintegrants, it could be argued that much work, perhaps most of the work, has already been done in the field of tablet disintegration.

This is possibly true, especially from the formulation standpoint; however, as far as the characterization work is concerned, many things still remain to be done and, quite importantly, the characterization efforts that are being done may be profitably exploited at least in two ways:

- for a more appropriate employment of disintegrants themselves
- in other fields of polymer application (see, for example, the exploitation of swelling polymers for controlling drug release).

In this paper, after briefly recalling some basic definitions and concepts, a few aspects of disintegrant characterization will be discussed.

As it has been stated in a very concise and efficient manner (1), solid dosage form disintegrants are excipients capable of overcoming the cohesive strength introduced by compression and binders. Possible mechanisms proposed for disintegrant action are: rapid water uptake into compacts, swelling of disintegrant particles, gas release, melting and enzymatic action.

Even though there has been a strong debate on that in the literature, swelling is probably the most widely accepted mechanism of disintegrant action (2-4).This is also due to the fact that particle swelling is directly linked to another claimed mechanism of disintegrant action, that is water uptake mechanism (5,6). In fact it has been definitely demonstrated by many excellent works (3,7,8) that an efficient swelling promotes a rapid water uptake into compacts.

The need for a better characterization of disintegrant swelling properties is dictated by a few considerations: first of all, by the development and the emerging use, a few years ago, of the so-called super disintegrants (9) and the need for a comparative evaluation of their functionality. An example of such a need is given by the so-called jungle of modified starches and celluloses, which represents a problem also as far as their employment as disintegrants is concerned. Furthermore it is desirable that, also in the case of disintegrants, both commercial and compendial specification settings are based not only on chemical purity and safety tests, but also on efficiency or "functionally relevant" (10) tests.

SWELLING PROPERTIES : EXTENT AND EFFICIENCY

In the opinion of a few authors (11,12) much of the controversy concerning the role of swelling in the disintegration process is due to the fact that some confusion has persistently been made between swelling extent and swelling efficiency.These two properties are not necessarily related to each other.

The methods for the quantitative evaluation of disintegrant swelling (swelling extent) may be grouped into: methods for the evaluation of intrinsic swelling, that is individual particle volume increase, and methods for the evaluation of swelling in bulk, that is water uptake capacity of disintegrant powder bed (8).

The former methods are mostly based on microscopic observation of particles (13), even though instrumental methods have also been proposed (14,15). These methods, with a few exceptions (8,16), mainly provide an evaluation of particle swelling in static conditions, that is at the equilibrium.

The latter methods may be, in turn, classified into: static methods, like hydration capacity (17) and sedimentation volume (9), and dynamic methods, like water uptake of powder bed (5,6), swelling of pure disintegrant tablets (7) and dilatometry (13).

Whereas static methods provide only for the quantification of the amount of water uptaken at the equilibrium, dynamic methods provide for the evaluation not only of the extent (amount of water uptaken or extent of expansion) but also of the rate of swelling process (2).

Unlike the methods for the quantitative evaluation of swelling, the approaches for the evaluation of swelling efficiency are far less common, although a few of them have been described in the literature. For instance, since the early 70ths, Couvreur et al. (18) talked about "energie du gonflement". List was the first who proposed to measurethe swelling pressure inside tablets (11,19); other authors, Colombo (20) and Gould (21), took up and exploited these concepts.

All the methods for the evaluation of swelling efficiency rely upon the measurement of a pressure or a force inside disintegrating tablets, meaning that they may be considered dynamic methods in the etymological sense of the word.

SWELLING EFFICIENCY: FORCE MEASUREMENTS IN COMPACTS

Our approach to the evaluation of swelling efficiency is based on the measurement of disintegrating (swelling) force that develops inside model tablets.

This investigation has been performed using the apparatus formerly described by Colombo (20) and further modified (4, 22), which allows disintegrating force versus time curves to be obtained and fitted according to suitable mathematical models that are capable of describing the phenomenon of force development.

First of all, the relationships between swelling of disintegrant particles and disintegrating force have been investigated and it has been demonstrated that it is not the extent of swellling but rather the type of interaction between the polymer and the penetrating medium that decides the amount of force developed (23).

Most importantly, the relationships between force development and disintegration properties have been examined and it has been concluded that the more meaningful force parameter with regard to disintegrating efficiency is the rate of force development (22).

In other words, a disintegrant is likely to be effective in a given formulation only when it promotes a rapid force development inside the compact (12).

These conclusions have been mostly achieved in formulations based on insoluble materials, where the only factor that promotes water uptake and force development is the presence of the disintegrant. Things tend to be more complicated in soluble formulations (24).

In order to deal with such complicated situations, some authors have come up with the idea of simultaneously measuring, in the very same tablet, the force developed and the water uptaken (25).

This approach should provide parameters that are suitable for quantifying capable of quantifying the ability of a disintegrant of efficiently transforming water into force and therefore allow a more intrinsic characterization of the disintegrant itself.

Two apparatus for the simultaneous determination of water uptake and force development have been described (25,26).The most meaningful information are drawn from the graph obtained by plotting the amount of force developed versus the amount of water uptaken (25). These force versus water curves are characterized by a sigmoidal shape, sometimes with a central linear portion that may extend over the entire duration of the phenomena (27). Typical examples of such curves are given in Figs. 1 and 2.

The parameter that has been thought to describe at the best the relationship between water uptake and force development is the derivative of the curve at the

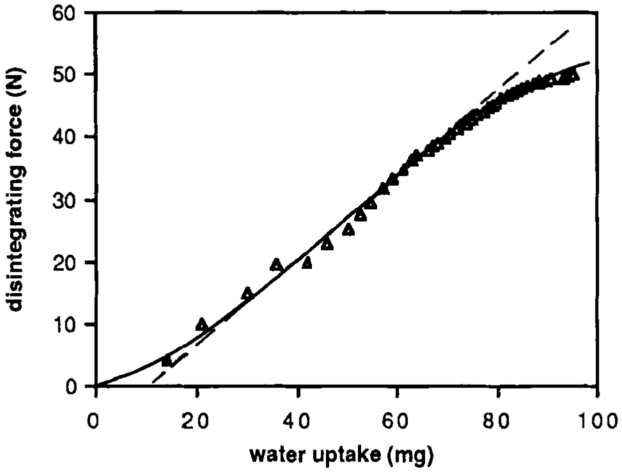

FIGURE 1
Force versus water curve of an individual dicalcium phosphate dihydrate tablet containing 5% of Primojel®

Δ : experimental — : fitted according to a sigmoidal model

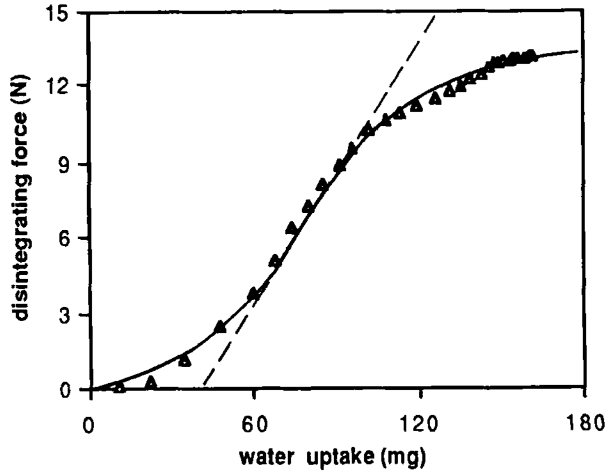

FIGURE 2
Force versus water curve of an individual dicalcium phosphate dihydrate tablet containing 5% of maize starch

Δ : experimental — : fitted according to a sigmoidal model

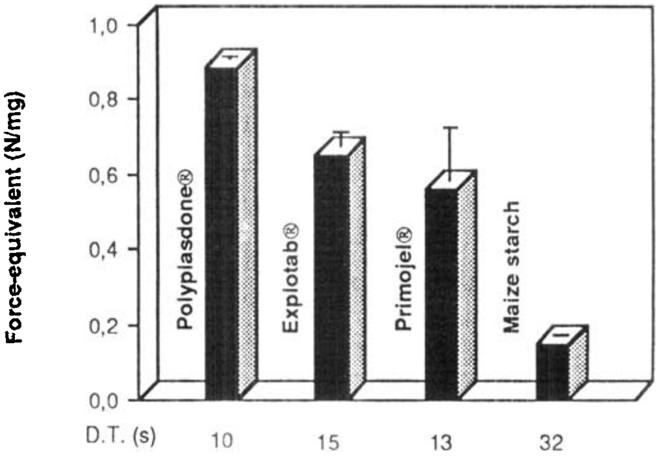

FIGURE 3
Comparison of force-equivalent values of four disintegrants
(D.T. = disintegration time)

centre of the sigmoidal distribution (see dashed line in Figg. 1 and 2), which corresponds to the maximum slope or to the slope of the so-called linear portion of the curve. This parameter,which is expressed in N/mg and named force-equivalent parameter, should express the maximum capability of a swelling agent of trasforming water into force and it has been proposed for the characterization of the efficiency of disintegrant swelling (27).

In Fig.3 the force-equivalent values of four different disintegrants that have been added in the same percentage (5% w/w) to the same recipe (dicalcium phosphate dihydrate) are compared; in particular a synthetic polymer (a crospovidone brand , Polyplasdone® XL) has been compared with two brands of sodium starch glycolate (Explotab® and Primojel®) and with a conventional starch (maize starch).

Significant differences have been found between the various types of disintegrants.

The high force-equivalent that has been found for crospovidone and sodium starch gycolate in comparison with maize starch are in line with the superiority of strongly swelling and highly hydrophilic disintegrants in insoluble formulations. Such differences are consistent with the differences in

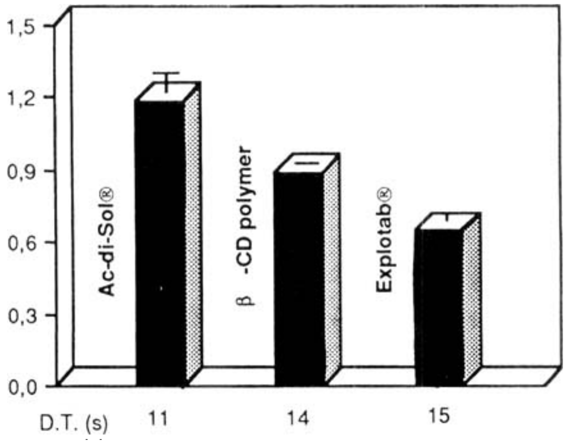

FIGURE 4
Comparison of force-equivalent values of three super-disintegrants (D.T. = disintegration time)

disintegrating efficiency as expressed by disintegration time. By the way, no significant difference has been observed between the two brands of sodium starch glycolate (Explotab® and Primojel®), as expected on the basis of their specifications.

Subsequently (Fig. 4) three different super disintegrants have been compared on the basis of the force-equivalent parameter in the very same recipe (dicalcium phosphate dihydrate) (28).

Despite comparable disintegration times, significant differences have been observed in the force-equivalent parameter between the various super disintegrants: the higher force-equivalent was obtained for croscarmellose (Ac-di-Sol®), then followed by β-CD polymer and sodium starch glycolate (Explotab®).

While the reasons for such differences still have to be investigated, it is noteworthy that the force-equivalent parameter allows the differentiation between swelling materials that are supposed to be equally effective.

It is believed that further investigation is needed. In particular the study of the force-equivalent that is expressed by a certain disintegrant in tablet recipes of different solubility and porosity should provide some sort of "fingerprint" of its efficiency.

SWELLING EXTENT - THE CASE OF LIMITED SWELLING MATERIALS

The second point that has recently been addressed by our research group is the quantification of intrinsic swelling in the case of the so-called limited swelling or non-swelling materials.

As above mentioned, it has been demonstrated that the swelling force depends rather more on the energy of swelling than on the extent of swelling, meaning that even limited swelling materials (sometimes called non-swelling disintegrants) can act as efficient disintegrants (12,23).

On the other hand, the difficulties of evaluating particle volume increase from microscopic data, especially in the case of limited swelling materials, are well known. This is especially true when particles are irregular in shape and their dimensions can be hardly evaluated by optical microscopy.

Another important consideration is that the swelling force developed by a disintegrant particle inside a compact also depends on its particle size in relation to the void size due to tablet porosity (19). This has recently been confirmed in the case of crospovidone (29) (Fig. 5).

Significant differences have been found between two commercial brands of crospovidone (Polyplasdone® XL and Kollidon® CL), as far as their disintegrating efficiency is concerned (Fig. 5).

When added in the same percentage (5% w/w) to the same base material (acetylsalicylic acid), the two brands produce different disintegration times, which are consistent with differences in force development rate inside tablets.

These differences may be attributed to the different particle size of the two commercial brands employed. In fact, when samples of the two brands having the same particle size (106-125µm) are employed, force development rate and disintegration time values are pretty much the same.

These considerations provide enough rationale for a thorough characterization of disintegrant particle size, both in swollen and in non-swollen state, and for the quantification of particle swelling. Such a characterization should be especially useful in the case of limited swelling materials.

With the aim of providing an alternative to optical microscopy, an instrumental method that is based on the employment of a Coulter Counter has recently been proposed (30) . This method allows the combined measurements of

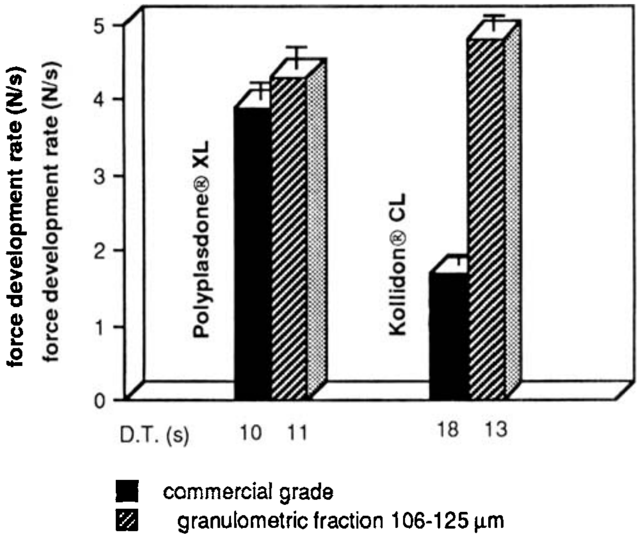

FIGURE 5
Influence of particle size of disintegrant on force development rate and disintegration time of acetylsalicylic acid tablets containing 5% (w/w) of crospovidone

particle volume increase (particle swelling) and granulometric characterization of disintegrants. The choice of the Coulter Counter method was advised by the fact that it provides facilities for counting and sizing particles and that its counting principle is on a volume basis, which should allow an exact calculation of particle volume. The measurements of particle swelling is based essentially on the comparison between calculated (from density) and measured (from the particle size distribution provided by a Coulter Counter) total particulate volume. The main problems are represented by the possibility of particle conductivity changes on swelling and by the accuracy of total particulate volume measurements.

Hereafter a few examples that illustrate the applicability limits of the method are given.

Basically, the first problem is related to the Coulter Counter operating principle: it is conceivable that, if particle conductivity changes on swelling, the Coulter Counter response may be impaired. To deal with this problem the method must be validated, either by optical microscopy (30) or by other granulometric techniques (laser diffraction, for example), in order to assess its applicability for the evaluation of particle swelling of a given swelling polymer in a given swelling medium.

In principle, if the Coulter Counter response were not impaired by conductivity problems, the mean particle diameter that is measured by a Coulter Counter should be pretty much the same as that measured by a laser diffraction apparatus, especially for particles that are not far from sphericity.

This is well the case of sodium starch glycolate particles in methyl alcohol, which acts as a non-swelling medium (Fig. 6).

The mean particle diameters obtained by a Coulter Counter (a) and a laser diffraction apparatus (b) are quite comparable, although the particle size distribution is slightly more skewed towards the large dimensions in the case of the laser diffraction method than in the case of the Coulter Counter method.This is well in line with the sizing principles of the two apparatus, which measure different equivalent diameters.These results are in line with those obtained by optical microscopy, meaning that the Coulter Counter method is applicable for sizing sodium starch glycolate particles in alcoholic medium.

In aqueous medium (e.g. isotonic saline) the results are quite different (Fig. 7).

The mean particle diameter obtained by the Coulter Counter method is much smaller than that obtained by the laser diffraction method and expected on the basis of microscopic observation (30).

Also the particle size distribution is markedly affected by the instrumental method employed; in particular in the case of the Coulter Counter method, the particle size distribution is considerably shifted towards the small dimensions, which is definitely due to the underestimation of swollen particle diameter.

This is in line with previous findings (30) and confirms that the Coulter Counter method is not applicable in the case of strongly swelling disintegrants, like sodium starch glycolate in aqueous medium.

The last example concerns the case of a crospovidone brand. Crospovidone is known to swell to a limited extent in many media, but , as already pointed out, it is difficult to judge the swelling extent from microscopic observation. The Coulter Counter method is believed to be applicable : in Fig. 8 the particle size distributions, which have been obtained by a Coulter Counter and a laser diffraction apparatus for a crospovidone granulometric fraction, are given.

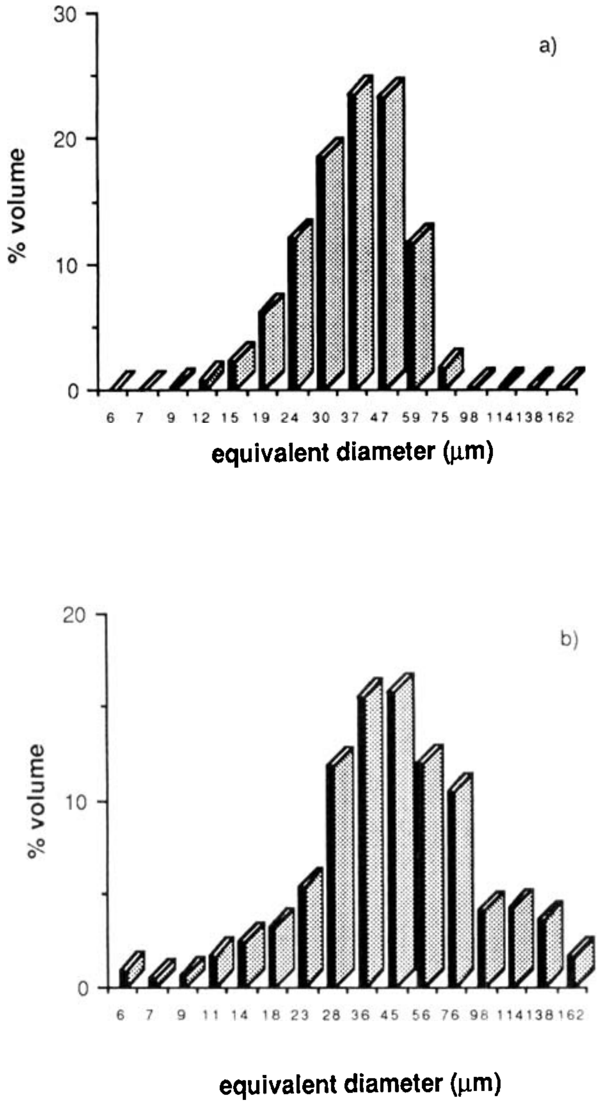

FIGURE 6

Size distribution of sodium starch glycolate particles in non-swelling medium (methyl alcohol)
a) Coulter Counter
b) laser diffraction

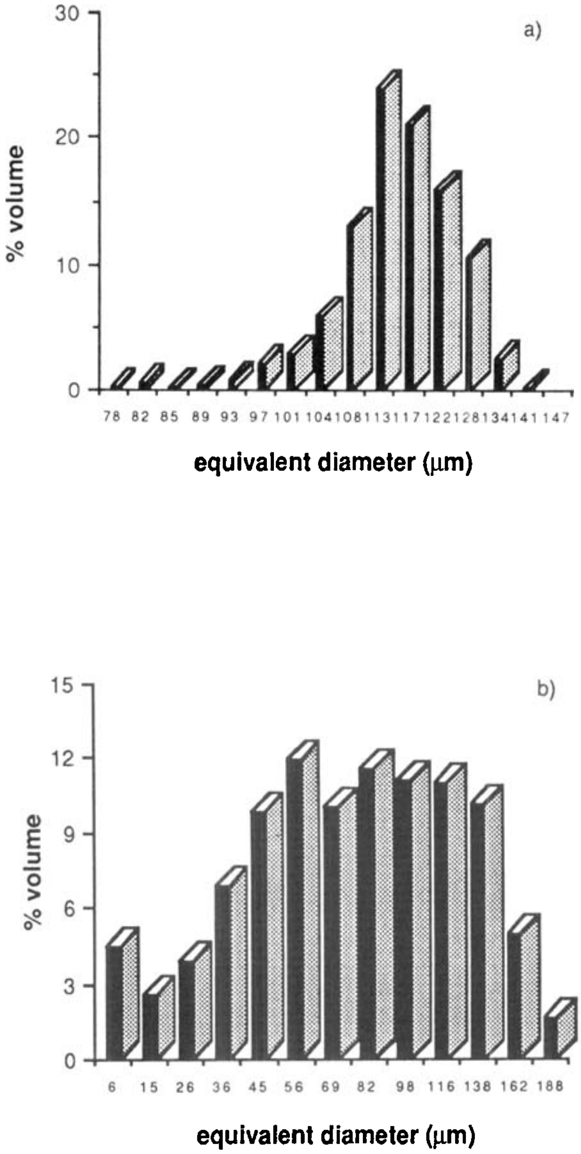

FIGURE 7
Size distribution of sodium starch glycolate swollen particles in aqueous medium (isotonic saline)
a) Coulter Counter
b) laser diffraction

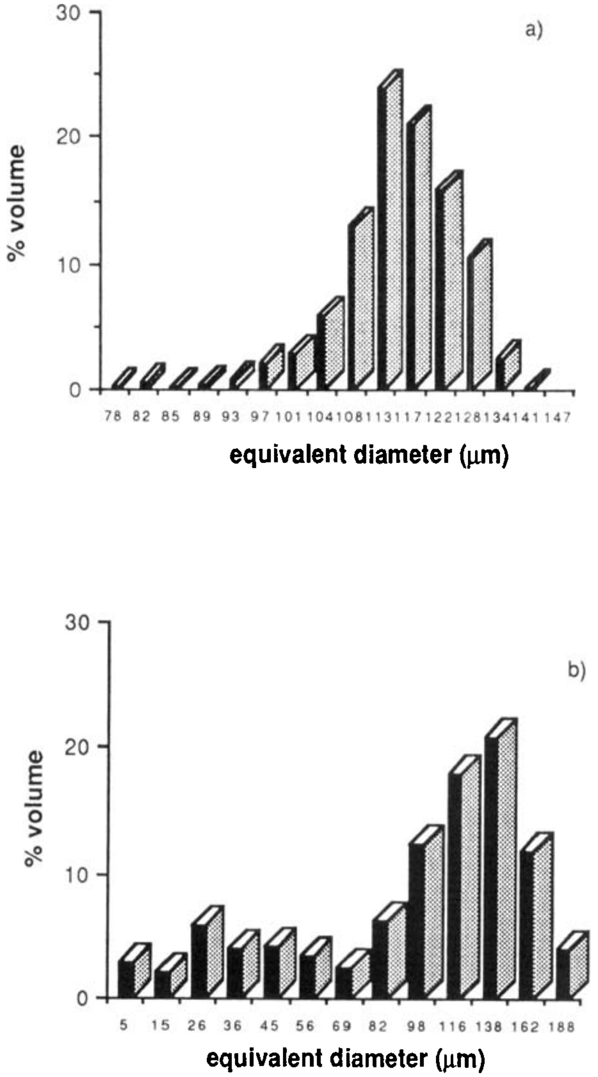

FIGURE 8
Size distribution of crospovidone particles (granulometric fraction 106-125 μm) in swelling medium (isotonic saline)
a) Coulter Counter b) laser diffraction

The mean particle sizes obtained with the two methods (~115 μm for the Coulter Counter and ~125 μm for the laser diffraction apparatus) are in good agreement especially if one considers the different sizing principles of the two apparatus and the fact that crospovidone particle shape is rather far from sphericity.

The particle size distribution obtained by the laser diffraction method is broader than that obtained by the Coulter Counter method (note that the size scales are different); this is in line with the fact that, with light interaction methods, particle orientation plays an important role in particle sizing and particles with rather high elongation or flakiness ratio tend to be overestimated.

On the other hand, the narrower particle size distribution obtained by the Coulter Counter method is in agreement with the microscopic data, which clearly showed the omodispersity of the material.

These results confirm the applicability of the Coulter Counter method for measuring the particle volume and particle volume increase of crospovidone particles in various media, both aqueous and non-aqueous, as already assessed in (30).

It must be remembered that the laser diffraction method provides particle size distribution on a volume basis but does not allow the direct calculation of the total particulate volume, from which the particle volume increase (particle swelling) may be calculated.

The Coulter Counter method was also found to be applicable in the case of another category of limited swelling materials, that is native starches (31). In this case, a particle swelling in aqueous media as low as 20% in volume has been reported in the literature (32), meaning that the accuracy of volume measurements provided by any instrumental method may represent a problem. The reliability of a method cannot indeed be guaranteed if the percentage accuracy of volume measurements is the same order of magnitude as the percentage volume change of the disintegrant particles.

The accuracy of the Coulter Counter method using different Coulter apparatus and therefore different channelizing and computational methods has recently been assessed (33). It has been concluded that, using a Coulter Multisizer apparatus, which allows a size resolution on 256 channels, volume measurements may be affected by an inaccuracy somewhere between 0 and 10%. Therefore volume changes greater than 10% can be estimated with sufficient accuracy.

Therefore the method is applicable to native starches, for which volume increases ranging from 20 to 60% have been reported in aqueous media (30-32).

The Coulter Counter method should also provide sufficient accuracy and flexibility in evaluating the volume changes of native starch particles in non-aqueous media (especially alcoholic media), which is still a matter of debate. To be able to quantify the swelling or shrinking of starch particles in various disintegrating media and to relate them to disintegrating properties should eventually allow a better understanding of the mechanisms of disintegrant action of natural starches.

CONCLUDING REMARKS

It has been mentioned at the very beginning that the endeavour at characterizing swelling disintegrants (in particular at describing water-disintegrant interactions in terms of disintegrating force parameters) could be exploited for characterizing other types of swelling polymers and solvent-polymer interactions.This has been already done, at least in part.

For instance the very same force measurements have been used for characterizing the swelling behaviour of film-coated swellable minimatrices (33).

The combined measurements of water uptake and force development have recently been employed for characterizing the porous structure of inert matrices containing ethylcellulose and for relating it to the drug release pattern (34).

Other applications of force measurements could be easily envisaged.

The task of developing such novel methods (based on the dynamic approach of force measurements) for disintegrant characterization has been considerably aided by computer facilities. Besides providing collection of both water uptake and force development data, computer aid is unique in allowing correction of experimental data and curve fitting according to suitable models, computation of model parameters and comparison of experimental curves on the basis of these parameters. The possibility of retrieving data from previous files and comparing new data with existing ones may also be exploited.

The software package provided is usually rather flexible and may be adjusted (by changing data collection conditions and by implementing new models) in order to deal with different materials and situations.

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