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Development of a New Software for an Interactive Analysis of Particle Size

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ABSTRACT

The aim of this work is to propose a new software for a more precise evaluation, computation, and visualization of characteristic parameters of particle size distribution. The software is created upon the building block concept, the outputs of each block being automatically connected to the other blocks, allowing a great level of interactivity. The principal characteristics printed or plotted are: (a) analysis menu (calculated outputs): summary tables of the aperture size of the sieves and their individual and cumulative associated percentage and corrected percentage, when a loss of powder occurs during the weighing of the different sieves; (b) graphic menu (calculated and plotted outputs): (i) bar chart of the individual percentages against the size of the sieves, (ii) Polygon of the cumulative percentages against the size of the sieves, (iii) Histograms and cumulative percentage polygon together, (iv) observed points evaluating the probit of the cumulative weight percentage against the logarithm of the aperture size of the sieves, (v) regression lines and their equation coefficients, (vi) the results of the chi-square test, associated to the calculation of the chosen regression equation, with its probability level and the interpretation of the test (linearity reject or linearity no reject), (vii) the mean diameter or diameter corresponding to any fractile and their confidence intervals, (viii) comparison between several regression lines, and (ix) friability test.

INTRODUCTION

Analysis of particle size is very important in defining essential characteristics of powder for their future uses. Granulation affects many fundamental properties of tablets such as disintegration, dissolution and bioavailability. Powder generally refers to the pharmaceutical dosage forms that are made of dry and solid material, more or less finely divided. The particle size of powders varies from the very fine to the coarse size. For example, very fine powders are used in aerosols and coarse powders are used in effervescent granules.

The relationship between particle size and many properties of drugs has been clearly established. Various chemical and physical properties of drug substances are affected by their particle size distribution and shapes, as well as their bioavailability.

With regard to technology, the particle size (or surface area) of solid drugs interferes with the flow properties of powders, their suspendibility, their compressibility, their organoleptic properties, and the stability of suspensions.

With regard to bioavailability, the particle size (or surface area) interferes with the rate of dissolution of drugs and the absorption rate of the drugs by the organism.

The purpose of this work is to propose a new software visualizing and calculating characteristic parameters of the particle size distribution with more accuracy, allowing interactivity. Some characteristics, like the mean diameter or diameter corresponding to any fractile (and their confidence interval), are computed. Graphical steps—like observed points evaluating the cumulative weight percentage probit against the sieve's aperture size logarithm, regression lines, and comparison of several regression lines—are also proposed.

ANALYSIS OF PARTICLE SIZE

Method

For determining granule size distribution, standard testing sieves must be employed. The different testing sieves are weighed and placed one upon another, in decreasing order of aperture size, and the column of sieves is placed upon a receiving pan. Some powder is introduced upon the column of sieves. This column is covered and placed on a shaker. After shaking, each sieve, as the receiving pan, is weighed.

Choice of Sieves

Four norms of aperture size of sieves are proposed:

- French Pharamcopeia norm
- French AFNOR NF-X-11-504 norm
- International ISO-R-565 or English BS-410:1976 norm
- American ASTM-E-11-70 norm

The French Pharmacopeia norm gives us assigned sieve size.Then, with this norm, we choose a series of seven consecutive sieves (except the receiving pan). The other norms enable us to select between three and eight aperture sizes of sieves, except the receiving pan. Every aperture size is keyed in, and the correspondence with the table of sizes, given by the norm, is controlled.

We compute the decimal logarithm ($\log_{10}$) of the aperture size of the sieves. We obtain an arithmetical progression. The notion of arithmetical progression ratio is a very important point for the graphical analysis of the particle size.

The arithmetical ratio of the logarithmic progression ($\log_{10}$[aperture size of the sieves]), according to the French Pharmacopeia norm and the French AFNOR NF-X-11-504 norm, is approximately constant, for all sieves, but not the ratio obtained with the ISO-R-565 (or English BS-410:1976 norm) and the American ASTM-E-11-70 norm. The invariability (or variability) of a ratio is handled by the graphical steps.

According to the three last norms, the user can select the aperture sizes of sieves. So, the user does not have to follow exactly the progression. The notion of "hole" in the series of sieves is introduced. A "hole" means a missing value for size of a sieve (or many sieves) in the series of sieves chosen by the user. The notion of "hole" is also handled for the graphical steps.

Data Entry

After the choice of the different sieves, there are there ways to enter data for an analysis of particle size:

1. Measurement of the difference between the weight of the sieves with and without powder, which gives the amount remaining on the different sieves: A summary table gives the different apertures of the sieves, the individual and cumulative percentages for each sieve. When a loss of powder occurs, the software adjusts ev-

ery individual percentage, to obtain 100% of cumulative percentage.
2. Calculation of the weight percentage: In this case, the user fills a table with the individual percentage. The software calculates the cumulative percentages during the filling of the table.
3. Use of a data file: The data files, resulting from the process of analysis of particle size, include each aperture size of sieve, each individual percentage, and the norm of aperture size of sieves used.

So, we can feed back these data into the process. A data file can be created after the process step that computes the equation of the regression line.

Decision Support for the Determination of the Series of Sieves

Method

As previously described, this software offers more flexibility. Furthermore, a decision support for the determination of the aperture size of the sieves is available. There are two steps for this decision support.

1. An analysis of particle size with assigned sieve sizes is made, scanning all the table of aperture sizes of sieves, corresponding to the selected norm. The aim of this step is the computation of the mean diameter, obtained with the assigned series of sieves.
2. The choice of a new series of sieves, computed around the mean diameter calculated at the end of the first step, is proposed.

Example

The selected norm is the French Pharmacopeia norm, so the assigned sieves sizes are: 4000, 2800, 1400, 710, 355, 180, and 90 μm. The user keys in the different weights, as described previously, and the software computes the regression line. The user can also reiterate the process, until the equation parameters become stable. After the regression processing, the software computes the mean diameter and its 95% confidence interval.

The mean diameter obtained by the first analysis is, for example, 340 μm. So, the proposed series is 1000, 710, 500, 355, 250, 180, and 125 μm. If we agree with the suggestion, a second particle size analysis can be undertaken.

Graphical Steps—Bar Chart and Cumulative Percentage Polygon

In all cases of norms, except the French Pharmacopeia norm, the graphical steps take into account the following facts:

- The notion of "weighting" associated to each ratio
- the notion of "hole," associated to the missing sieves, in a series
- the notion of "area" on the graphic with each aperture size of the series, directly linked with the weighting and the "hole"

Bar Chart

We have plotted the individual weight percentages against the distribution size of the sieves. The wideness of the histograms is independent of the number of sieves. So, the wideness of each bar is adjusted. The wideness depends on three facts:

1. The number of sieves used in a series, more exactly the sum of the consecutive sieves between the minimal aperture size and the maximal aperture size, also including possibly "holes" in the progression of the series.
2. The weighting associated to the ratio of the logarithmic progression of the sieve sizes. When the weighting associated to an aperture size is greater than 1, fictive holes replace the remaining weighting.
3. The width of the histogram, which is invariable.

The height of each bar is proportional to the weight percentages that fill within the interval.

Cumulative Percentage Polygon

We have plotted the cumulative weight percentages against the distribution size of the sieves. The software shows the sum of the percentages for all classes. The last polygon side reaches 100%.

Bar Chart and Cumulative Percentage Polygon Together

Bar chart and polygon can be plotted together, in order to give a best estimation of the representation of the weight percentages (individual and cumulative together) against the distribution size of the sieves.

Graphical Adjustment

If we want a correct histogram, every class must be represented by a bar, the area of which, and not the height, is proportional to the weight percentage. The area takes into account the width between two sieves in logarithmic scale and the possibility of holes, when the series of sieves chosen by the user do not follow the progression. Graphically, it is possible to have the right distribution. If a hole is encountered, the bar height is divided by a certain ratio, to obtain the right area, filling this hole.

An example, with the American norm, is given in Fig. 1, Fig. 2, and Table 1 (simulated data).

Graphical Steps—Regression Lines

To characterize the particle size distribution, we compare the data to the theorical log normal distribution. We can consider that the particle size follows a normal distribution against the logarithm of aperture sizes. So, after a probit transformation, the cumulative curve becomes a straight line.

To calculate the line equation, we must use an iterative method, because probit(0) and probit(1) are not defined. Firstly, the equation is calculated without these two points. Then, we can reintroduce them, to have the final equation of the regression line, when the parameters of the equation become stable.

The goodness of fit is computed by the chi-square test, significant level is fixed at 5%, and we set the confidence interval at 95%; degree of freedom (*df*) is equation to $n - 2$ (n: number of sieves). The software furnishes an interpretation of this statistical test: *linearity* of the straight line (hypothesis) is *rejected* or *not rejected*. At the end of the procedure, the mean diameter or the diameter corresponding to any fractile is given, with the confidence intervals.

After these steps, the parameters of the analysis (norm used, number of sieves, aperture size of the sieves with their individual weight percentages, and the coefficients of the regression line), and other intermediate parameters (ratios and so forth) used for the computation, can be saved on disk. A name can be chosen for the data file (8 characters maximum with the MS-DOS® operating system). So, the data file is written on disk as: [Name on file].GRN. An example is given in Table 2 and Figs. 3 and 4.

At any time, the observed points and the calculated lines (Figs. 3 and 4) can be set up. The coefficients of the equation are stable after the seventh iteration, as shown in Fig. 4.

The hypothesis of linearity is not rejected and gives us the mean diameter (50%):249 μm, the diameter corresponding to 75% fractile and the diameter corresponding to 25% fractile (Tables 3, 4, and 5).

Graphical Steps—Comparison of Two Regression Lines

Aim

The comparison of two regression lines is used for the friability test. Before compressing a mixing powder,

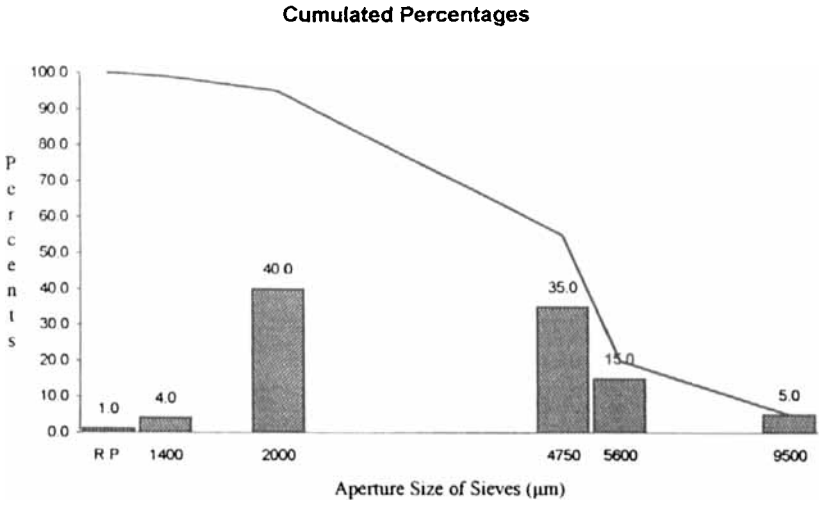

Figure 1. Bar chart and cumulative percentage polygon before adjustment.

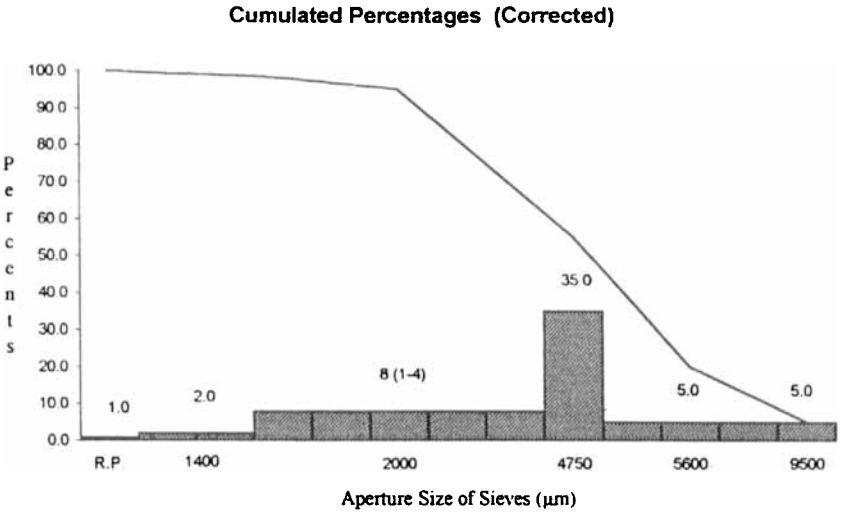

Figure 2. Histogram and cumulative percentage polygon after adjustment.

Table 1

Series of Sieves Chosen—Position Taken on Graphic; Individual Weight Before and After Adjustment

Aperture Size of Sieves	Height in Bar Chart (%)	Ratio of the Progression		Height in Histogram (%)	Area
9500 µm	5	1		5	5% × 1 (5%)
5600 µm	15	3		5	5% × 3 (15%)
4750 µm	35	1		35	35% × 1 (35%)
Hole	0	4	}	8	8% × 5 (40%)
2000 µm	40	1			
1400 µm	4	2		2	2% × 5 (4%)
Receiving pan	1	1		1	1% × 1 (1%)

Table 2

Analysis of Particle Size with the P4105V.GRN Data File (French Pharmacopeia)

Series of Sieves	Weight Percentage	Cumulative Percentage
Sieve 1 ≥ 710 µm	3.28 %	3.28 %
Sieve 2 ≥ 500 µm	4.62 %	7.90 %
Sieve 3 ≥ 355 µm	4.42 %	12.32 %
Sieve 4 ≥ 250 µm	19.10 %	31.42 %
Sieve 5 ≥ 180 µm	37.33 %	68.75 %
Sieve 6 ≥ 125 µm	23.79 %	92.54 %
Sieve 7 ≥ 90 µm	6.50 %	99.04 %
Receiving pan	0.96 %	100.00 %

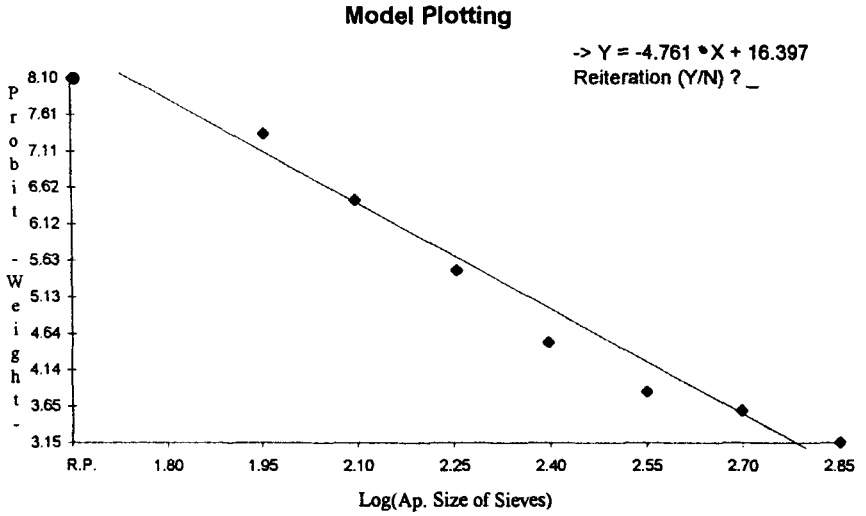

Figure 3. Observed points and first regression line.

Table 3

Conclusions and Computation of the Mean Diameter

Modeling—straight line of Henry
Equation of the straight line: $Y = -4.874057 \times X + 16.68219$
Chi-square test = 0.7908 $df = 6$ Linearity: NO REJECT
Log(diam 50%):2.396811 $SD = 7.459395E\text{-}02$
Diam 50% = 249 μm 95% CI: [178, 349]

Table 4

Conclusions and Computation of the Diameter Corresponding to 75% of Amount of Powder

Modeling—straight line of Henry
Equation of the straight line: $Y = -4.874057 \times X + 16.68219$
Chi-square test = 0.7908 $df = 6$ Linearity: NO REJECT
Log(diam 75%): 2.258431 $SD = 7.315493E\text{-}02$
Diam 75% = 181 μm 95% CI: [130, 252]

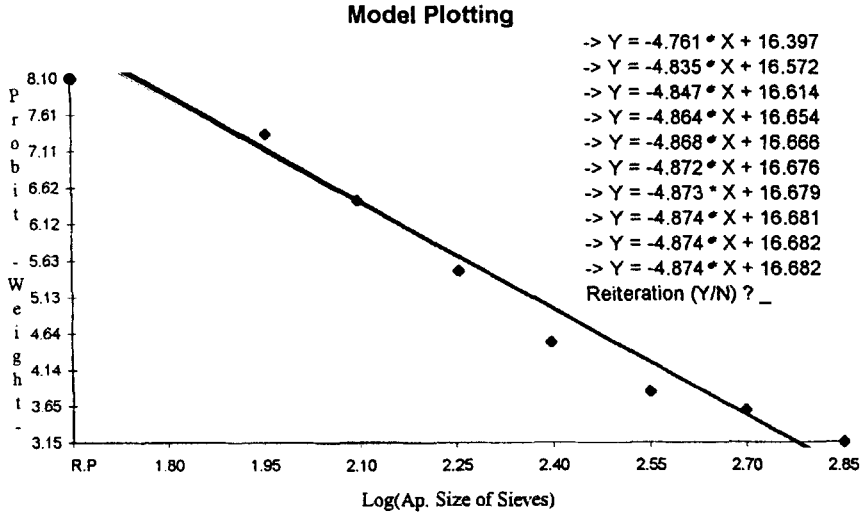

Figure 4. Observed points and model plotting after 8 iterations.

Table 5

Conclusions and Computation of the Diameter Corresponding to 25% of Amount of Powder

Modeling—straight line of Henry
Equation of the straight line: $Y = -4.874057 \times X + 16.68219$
Chi-square test = 0.7908 $df = 6$ Linearity: NO REJECT
Log(diam 25%): 2.535195 $SD = 8.497979E\text{-}02$
Diam 25% = 343 μm 95% CI: [234, 503]

different tests must be performed, for the evaluation of its fluidity, packing, mean diameter and its granulometric distribution, and friability. The friability test brings data about the degree of manipulation of the particle (a high indicator of friability is a sign of its adulteration) and the limit values of the grain, to obtain the best quality of tablets and the influence on friability of the binding agents. The software uses the method of Rubinstein (5), with adaptation. The Friability Index is calculated as below:

$$\text{Friability Index} = \left[1 - \left(\frac{\text{mean diameter after the test}}{\text{mean diameter before the test}}\right)\right] \times 100$$

An analysis of particle size of mixing powder is processed before the friability test. The friability test consists in placing the powder in a friabilator. Thereafter, we make a second analysis of the particle size of the mixing powder. This method gives the mean diameter before and after the test. If the mean diameter of the grain after the test is much lower than the mean diameter before the test, the Friability Index is very high. In other words, the grain is highly friable, also adulterating. A Friability Index reaching 0% corresponds to a nonfriable grain.

Conditions to Propose the Friability Test

These conditions are fixed by the results of the comparison of the slopes and the intercepts. If the comparison of the two slopes *confirms the hypothesis of the parallelism of these slopes*, a comparison of the intercepts is made. If the result of the comparison of the two intercepts confirms (or not) that *the intercepts are identical*, we propose a friability test.

The hypothesis of parallelism of two slopes and identical intercepts shows us that the two lines are identical. In this case, the test is very important to appreciate the low degree of friability of the grain.

The hypothesis of parallelism of two slopes and not identical intercepts shows us that the two lines are not merged but really parallel, corresponding to an *unwedging* of the lines. So, a friability test, with these results, is very important to appreciate the behavior of the grain, in other words, its high degree of friability.

Method

We use data files to overlay the two regression lines. The user keys in the name of these files. To make the friability test, the names of the files that are used correspond to the analysis of particle size before the test and to the analysis after the test. A graphical display is proposed, showing the lines with their equations. The procedures of slopes and intercepts comparison are classical (Student's test).

Example

Data files are named P4105V.GRN (before the friability test) and P4105VA.GRN (after the friability test). The summary tables are printed; the two regression lines are parallel and the intercepts are not different, as shown in Fig. 5. This hypothesis is also confirmed with the statistical procedures. The friability test gives us a Friability Index equal to 12.05. In this case, the grain is not very friable (Table 6).

Graphical Steps—Comparison of Several Regression Lines (between 3 and 5)

A plot of several regression lines is proposed. We can see, with this chart, the different tendencies of the lines. The summary tables, corresponding to each data file, are printed before the chart.

DATA-PROCESSING ASPECTS

Outline Flowchart (overall block diagram)

The flowchart is shown in Fig. 6.

Print Process

At any time, the user can print the display screens with the print process of the software. The print process is just a graphic hard copy. If the user wants to print a display screen to the printer or plotter, he uses the function key "Print Screen." To use the graphic hard copy,

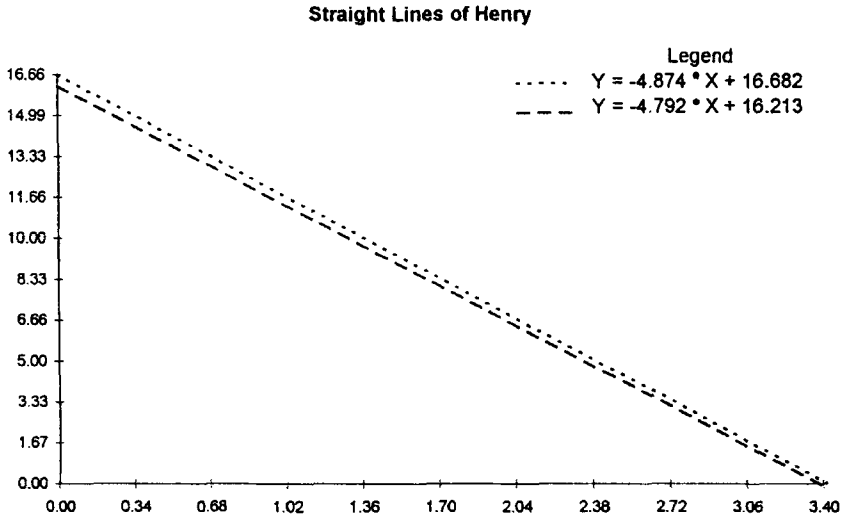

Figure 5. Comparison of two regression lines (files P4105V.GRN and P4105VA.GRN).

we must make a printer configuration, with the MS-DOS command GRAPHICS, before running the software. The syntax of the command is: GRAPHICS [name of configuration file]. The configuration file allows printing of special characters (such as graphical characters) with the printer or plotter.

Material

The software runs on IBM PC or compatibles, with these characteristics:

- Capacity of RAM 640 kilobytes or more
- Microprocessor Type Intel 80286 or later
- Graphic adaptator CGA, VGA, or SVGA

Table 6

Results of the Slopes and Intercepts Comparison

Test of comparison of the slopes
Student's test: 0.0349 with *df*: 12
Parallelism of the slopes: *NO REJECT*
Test of comparison of the intercepts
Student's test: 0.0518 with *df*: 12
Identical intercepts . . .: *NO REJECT*
Friability test
Friability Index = 12.05

- Disk space required for the software 150 kilobytes
- Disk space required for the data files 450 bytes per file

The software requires less than 150 Ko on hard or floppy disk. The source code is written with the Microsoft® Quick Basic v.4 language and the software is compiled. This software runs also in the Windows® environment. The program file is named Granulo.Exe.

Data Files

The saved files, created after the computation of the regression lines (regression lines block), are ASCII files, including:

- A number giving the chosen norm
- The number of sieves constituent of the series
- The aperture size of each sieve
- The position of each sieve in the series of sieves included in the software
- The individual weight percentage of each sieve
- The logarithm of the aperture size of each sieve
- The probit of each weight percentage
- The coefficients of the regression line
- The mean diameter, if this mean diameter is computed

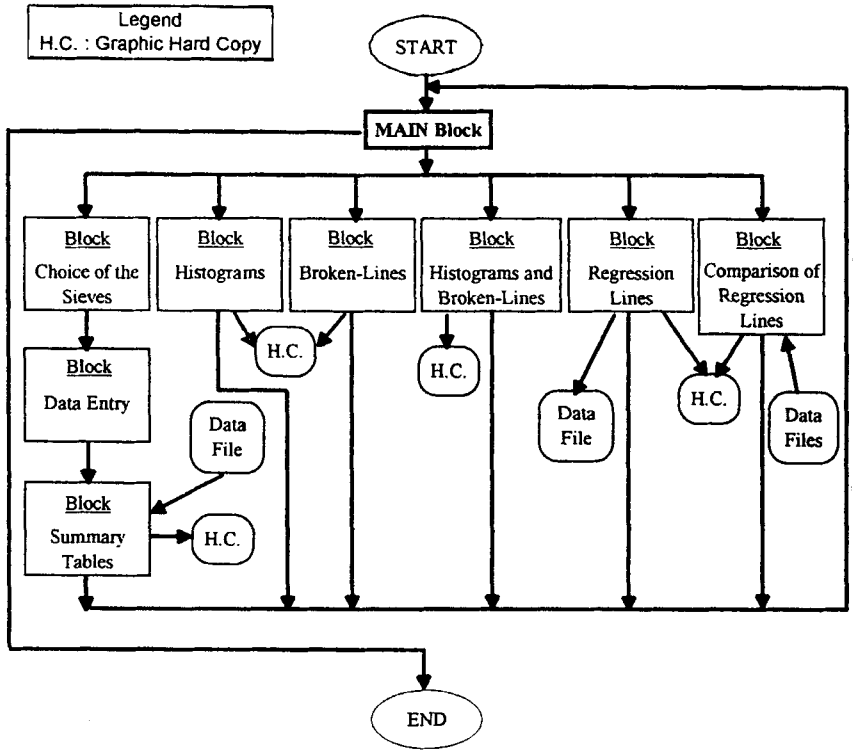

Figure 6. Outline flowchart.

It is very easy to obtain the content of a data file, with the MS-DOS command TYPE. The syntax of this command is TYPE [name of the data file]

DISCUSSION AND CONCLUSION

This software was tested with many records from studies in wet granulation. It offers a useful method for the measurement of particle size with, for example:

- The support of different norms of aperture size of sieves.
- The flexible data entry mechanism: by data files or with the keyboard, with control in line.
- The ability to produce customized graphs. At each step, the titles of the graphs, and the title of the x and y axis can be changed.
- The ability to overlay observed points and calculated regression lines.
- The statistical tests associated to the regression modeling, and the interpretation of these tests.
- The comparison of several regression lines, making it possible to estimate graphically the behavior of these lines. In the case of two regression lines, the comparison of the slopes and intercepts is proposed.
- The possibility of listing the data files. These files can also been read from other software.

The most recent version seems to work satisfactorily, but we hope to bring some improvements, such as computerizing the statistical process for comparison of more than two regression lines and introducing the notion of "weighting" associated with each point (x: log(aperture size), y: probit of the cumulative weight percentage), because we think that each point does not have the same impact (exactness) for the process of calculation of the regression line. The different points do not have the same accuracy.

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