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Validation of particle size distribution in pharmaceutical excipients

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ABSTRACT

Particle size distribution is a critical feature of the drug development process. It influences manufacturability, pharmaceutical elegance product performance and formulation. The particle size distribution of a pharmaceutical ingredient or product is often described by a log-normal distribution from which a single representative number, such as mean or median particle size is usually derived and reported. The aim of the study was to elucidate a correlation between the quantitative statistical micromeretic parameters of pharmaceutical powders in order to validate the particle size distribution. Pharmaceutical powders are quantized by coefficient of skewness (IQCS) and coefficient of kurtosis (β2) determination and the correlation between the two statistical parameters was assessed. The third and fourth moments, descriptors of skewness and kurtosis, may be used to test the hypothesis that the sample came from a normal distribution. Particle size analyses of the powders were carried out by microscopic technique using eye piece micrometer. Around 600 particles were counted avoiding the aggregates and the data obtained was plotted as frequency distribution curve and cumulative frequency distribution curve. All the powders showed asymmetric particle size distribution as their IQCS values were observed .

Keywords: Coefficient of skewness and kurtosis, microscopic technique, eye piece micrometer

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INTRODUCTION

Powders are important in the development of pharmaceutical products since many formulations either are powders or contain powders[1-3]. Particle size measurements in pharmaceutical sciences are performed using such techniques as optical scattering (laser diffraction, dynamic light scattering), particle counting (electrical, optical) and ultrasonic spectroscopy. These methods offer the advantage of high throughput analysis, repeatability, and regulatory recognition. Ideally, the particle size results are normally distributed such that the mean, median and mode are equal. Skewness measure the symmetry of the distribution about the mean; a right skewed distribution would have significantly more coarse particles in the distribution while a left skewed distribution would have significantly more fines. Kurtosis is a measure of how concentrated the distribution is relative to the mean. A distribution which significantly steep sides (hence peaky) would be described as having excess kurtosis. Adopting skewness and kurtosis for particle size specifications would require a robust universal standard for data processing and interpretation. The conventional calculations for skewness and kurtosis (as cubic and quadratic functions of the distribution mean) have been criticized for their sensitivity to outliers and have consequently been described as lacking robustness[4,5]. Robust alternatives for evaluating distribution asymmetry have been proposed. Kim and white presented an alternative evaluation for skewness and kurtosis based on interquartile ranges of the distribution.

Huang and Ku proposed an asymmetry parameter based on a logarithmic function with the 10^{th}, 50^{th} and 90^{th} percentiles of the distribution. Blott and pye have recommended the graphical model of folk and ward as a robust alternative to evaluating skewness and kurtosis as the 3^{rd} and 4^{th} moments of the distribution mean. The particle size distribution can be defined both qualitatively and quantitatively. Quantization is possible by summarizing the distribution data by statistical methods the degree of skewness of the particle population may be defined by IQCS (Inter quartile coefficient of skewness).

IQCS can be determined by the following equation,

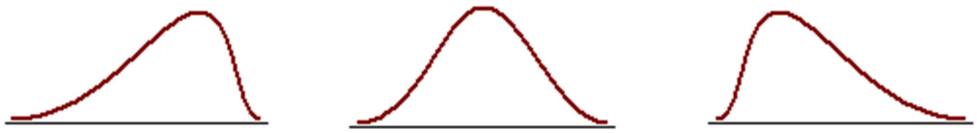
$IQCS = (Q_3-Q_2)-(Q_2-Q_1)/Q_3-Q_1$

Where Q_2 is the middle quartile point Q_1&Q_3 are the lower and upper quartile points. The value of IQCS lies between -1 to +1 and for symmetrical particle size distribution IQCS is zero. IQCS is used for the assessment of a spectrum of roughness and imaging characterization of different pharmaceutical surfaces and assessment of solid delivery systems for controlled release cascade impactor profiles of pharmaceutical aerosols for testing the sensitivity of hyperspectral imaging instruments in oral dosage forms. Coefficient of kurtosis is the other statistical parameter used to quantify the degree of symmetry of particle size distribution[6-8].

Skewness:

The coefficient of Skewness is a measure for the degree of symmetry in the variable distribution.
Skewness quantifies how symmetrical the distribution is,

- A symmetrical distribution has a skewness of zero.
- An asymmetrical distribution with a long tail to the right (higher values) has a positive skew.
- An asymmetrical distribution with a long tail to the left (lower values) has a negative skew.
  The skewness is unitless.
-
  Any threshold or rule of thumb is arbitrary, but here is one: If the skewness is greater than 1.0 (or less than -1.0), the skewness is substantial and the distribution is far from symmetrical.



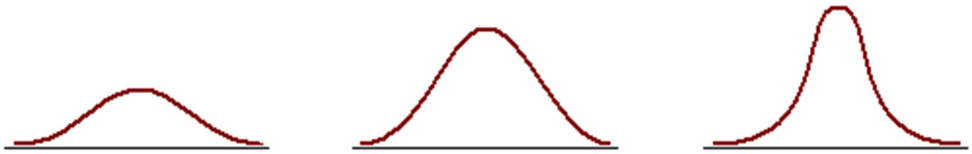
Negatively skewed distribution or Skewed to the left Skewness <0

Normal distribution Symmetrical Skewness = 0

Positively skewed distribution or Skewed to the right Skewness > 0

Kurtosis:

Coefficient of kurtosis is denoted by β. It can be determined by $\beta_2=\mu_4/\mu_2^2$ where μ_2 is the second moment about mean & μ_4 is the fourth moment about mean.The coefficient of Kurtosis is a measure for the degree of peakedness/flatness in the variable distribution. The value of β_2 lies between -3 to +3.



Platykurtic distribution Low degree of peakedness Kurtosis <3

Normal distribution Mesokurtic distribution Kurtosis = 3

Leptokurtic distribution High degree of peakedness Kurtosis > 3

Skewness and kurtosis are terms that describe the shape and symmetry of a distribution of scores. skewness and kurtosis only serve as descriptions of the distribution of your data. Skewness refers to whether the distribution is symmetrical with respect to its dispersion from the mean. If on one side of the mean has extreme scores but the other does not, the distribution is said to be skewed. Kurtosis refers to the weight of the tails of a distribution[9,10].

MATERIALS AND METHODS

The following powders are used γ-CD, Polyplasdone CPXL, Metolose 90SH, HP β -CD, Cross linked polymer(Ac-di-sol), Metolose, ECT-10, MCC(Avicel), Methocel K100.
Particle size analyses of the powders were carried out by microscopic technique using eye piece micrometer. Around 600 particles were counted avoiding the aggregates and the data obtained was plotted as frequency distribution curve and cumulative frequency distribution curve.

Calculation of IQCS and β_2
IQCS & β_2 was caluculated by using the equation ,

$IQCS=(Q_3-Q_2)-(Q_2-Q_1)/Q_3-Q_1$

whereQ_2 is the middle quartile point Q_1&Q_3 are the lower and upper quartile points.
$\beta_2=\mu_4/\mu_2^2$ where μ_2 is the second moment about mean & μ_4 is the fourth moment about mean.

RESULTS AND DISCUSSION

Nine pharmaceutical powder samples categorized as Solubilising agent (γ-CD), HP β -CD) , Disintegrant (Polyplasdone CPXL) , Binder(Metolose 90SH) , Superdisintegrant (AC-DI-SOL), Thickening agent (Metolose), Coating agent (ECT-10), Diluent (MCC (Avicel), Coating agent(Methocel k100) were subjected to microscopic particle size analysis to get the particle size distribution data.

Table 1: Comparative Statistical Parameters of Different Powder Samples

S.NO	Sample Powder	Category	IQCS	β_2
1	γ-CD	Solubilising agent	0.375	3.69
2	Polyplasdone CPXL	Disintegrant	-0.46	1.27
3	Metolose 90SH	Binder	-0.125	2.75
4	HP β -CD	Solubilising agent	0.27	1
5	Cross linked polymer (Ac-di-sol)	Superdisintegrant	0.28	2.49
6	Metolose	Thickening agent	0.3	2.249
7	ECT-10	Coating agent	0.17	2.2
8	MCC (Avicel)	Diluent	0.322	1.098
9	Methocel K100	Coating agent	0.29	2.65

Figures 1 - 6: Frequency distribution curve graphs for nine excipients

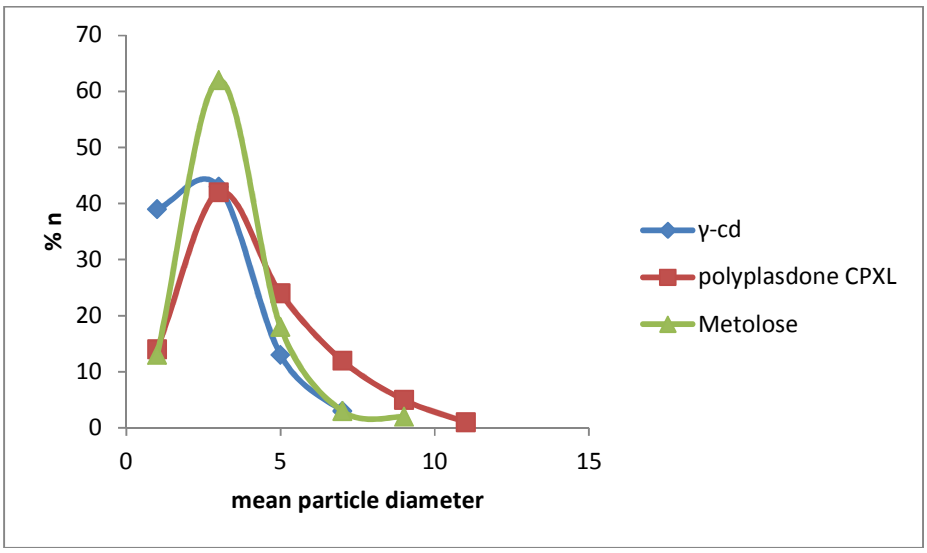


Fig.1

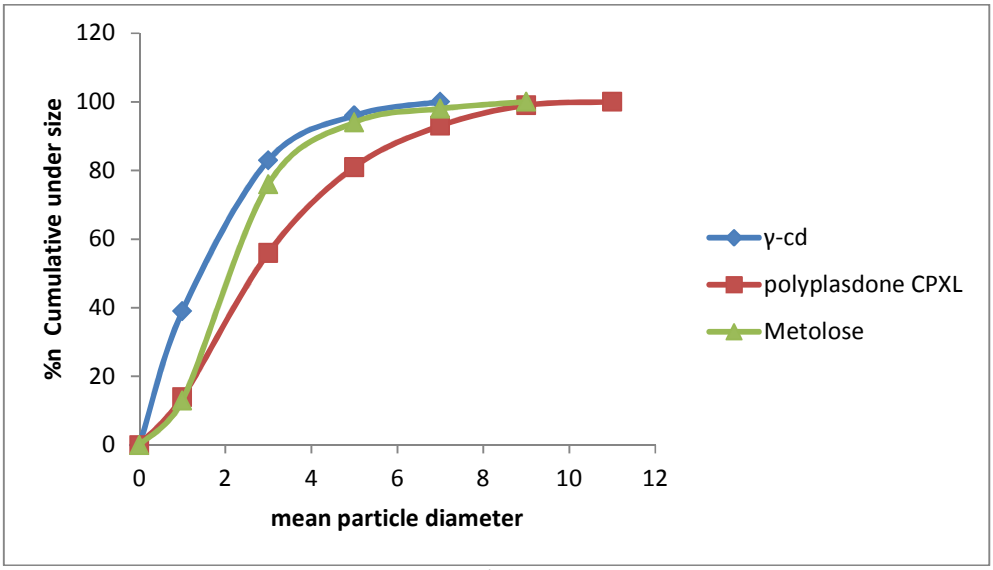

120
100
80
60
40
20
0
%n Cumulative under size
0
2
4
6
8
10
12
mean particle diameter
γ-cd
polyplasdone CPXL
Metolose

Fig.2

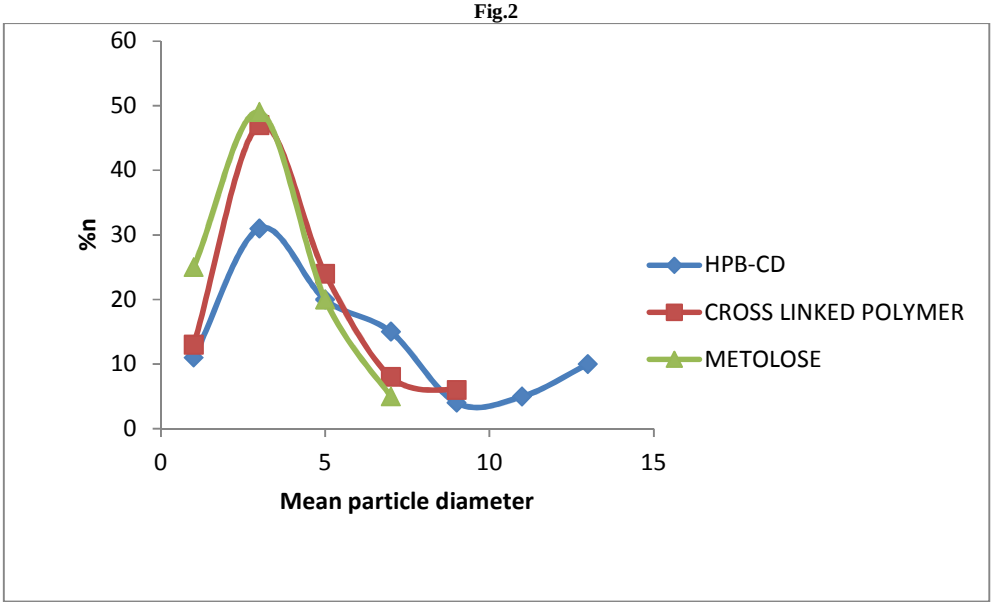

60
50
40
30
20
10
0
%n
0
5
10
15
Mean particle diameter
HPB-CD
CROSS LINKED POLYMER
METOLOSE

Fig.3

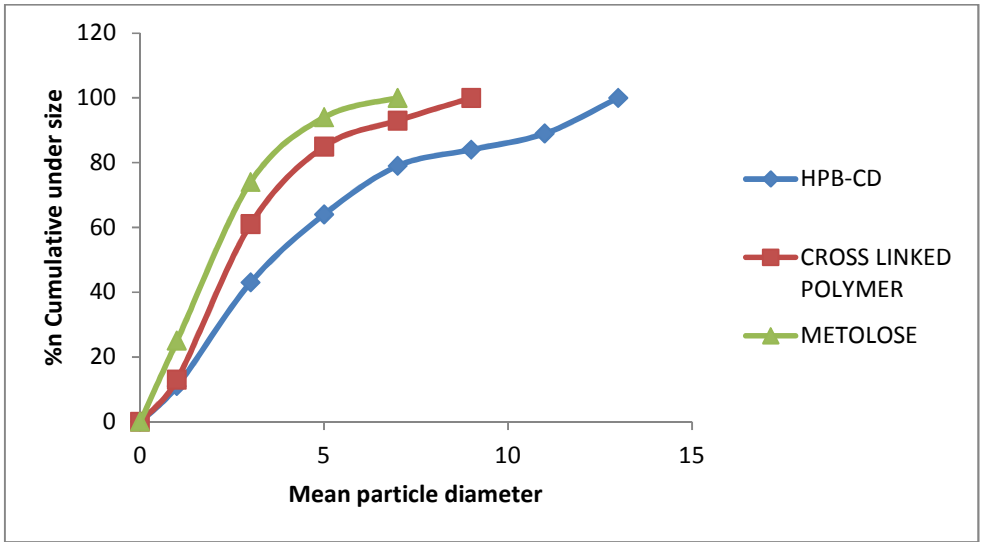

120
100
80
60
40
20
0
%n Cumulative under size
0
5
10
15
Mean particle diameter
HPB-CD
CROSS LINKED POLYMER
METOLOSE

Fig.4

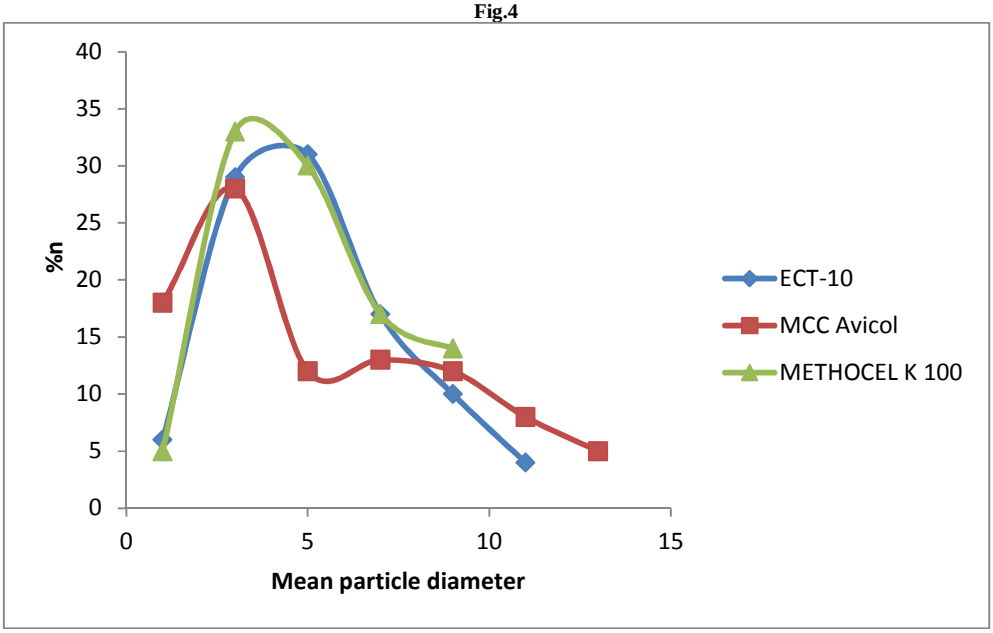

40
35
30
25
20
15
10
5
0
%n
0
5
10
15
Mean particle diameter
ECT-10
MCC Avicol
METHOCEL K 100

Fig.5

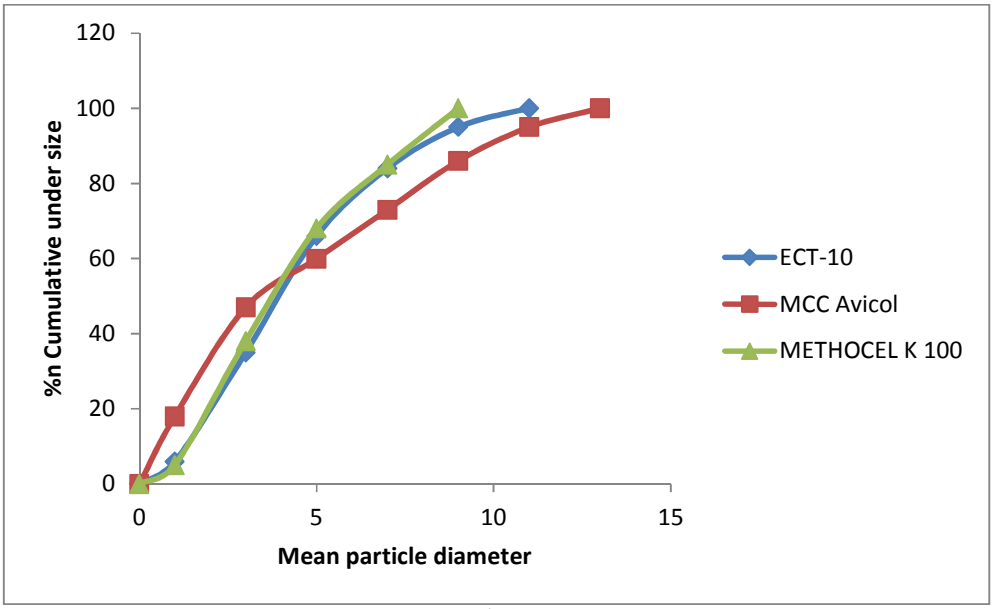


Fig.6

Frequency distribution curve graphs for nine different categories of excipients exhibited positive skewness for γ-CD, HP β -CD, Metolose, Methocel, Crosslinked polymer, MCC(Avicel). Negative skewness for Polyplasdone, Metolose 90SH are shown in **Figures 1-6**. A normal frequency distribution is obtained by ECT-10. Quantitative statistical analysis of the data was done to get the value of IQCS and β_2 and results obtained are summarized in **Table 1**. All the powders showed asymmetric particle size distribution as their IQCS values were observed to be greater than zero for γ-CD, HP β -CD, Metolose, Methocel, Crosslinked polymer, MCC and less than zero for Polyplasdone, Metolose 90SH. β_2 values less than three for Metolose 90SH, HP β -CD, Methocel, Cross linked polymer, ECT-10, Metolose, Polyplasdone, MCC suggest platykurtic distribution. Leptokurtic distribution is favored by β_2 values greater than three for γ-CD.

CONCLUSION

Particle size analyses of the pharmaceutical excipients were carried out by microscopic technique using eye piece micrometer. Around 600 particles were counted avoiding the aggregates and the data obtained was plotted as frequency distribution curve and cumulative frequency distribution curve. All the excipients showed asymmetric particle size distribution as their IQCS values were observed. The results obtained are indicative of a preliminary study which needs to be further worked out with more experimentation to confirm the results and are in progress in our laboratory.

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