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Research Article

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Analysis of Particle Size Distribution of Some Powders and Dosage Forms by Skewness and Kurtosis

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ABSTRACT

For pharmaceutical powders it is unusual to be completely monosized as they are frequently processed by milling or precipitation and hence they contain range of particles with different shapes and sizes. These factors of solid dosage form i.e. particle size and shape are known to alter the product performances like content uniformity, characteristics, solubility, stability and consequently therapeutic efficacy along with its pharmaceutical elegance and product performance. For better handling of manufacturing process and other parameters it is important to determine the particle size distribution (PSD) of pharmaceutical powders. PSD is often described by log-normal distribution; this single parameter is stastically insufficient. Inter Quartile Coefficient of Skewness (IQCS) and Coefficient of kurtosis (β_2) values of powder samples were calculated and then subjected to linear regression. Correlation is made for both the stastical parameters. Thus establishing a correlation between the two parameters may be used as an additional validation parameter to quantitate the particle size distribution data for set of powders and may serve as useful tool for pharmaceutical processing. Drug development practitioners can adopt for information purpose only with the objective of developing knowledge space on utility, variability and robustness of chosen approach. In the present work, four dosage forms (microspheres, niosomes, solid dispersions and polymorphs) were prepared with variable process parameters and were compared for IQCS and β_2 with in vitro dissolution studies. IQCS and β_2 were calculated by using a simple computer program developed by us and reported.

Keywords: Inter quartile coefficient of skewness; Coefficient of kurtosis; Microspheres; Niosomes; Solid dispersions; Polymorphs

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INTRODUCTION

The pharmaceutical industry pays much attention to the role and variability of the physical properties of particulate material, not only active ingredients, but also pharmaceutical powders [1]. Pharmaceutical powders are usually polydisperse with variable particle size and shapes thus it is necessary to know not only size of particles but also how many particles exist in the sample. Most often a powder is composed of three types of particles, elementary particles, aggregates and agglomerates and offers a variety of particle size and particle shapes. Particles of different sizes in a given powder have different flow and packing properties that tend to alter the volume of powder during encapsulation or tablet compression event [2]. In the pharmaceutical powders and solid dosage forms, particle size and shape are known to affect the product performances including processing characteristics, content uniformity, solubility, stability, bioavailability and consequently therapeutic efficiency. For better handling of manufacturing process it is important to determine the particle size distribution of the pharmaceutical powders. Quantization of the

particle size distribution can be done by defining various related statistical parameters namely coefficient of kurtosis (β_2), interquartile coefficient of skewness (IQCS) and Yule coefficient of Skewness [3].

Inter Quartile Coefficient of Skewness (IQCS)

Skewness is a measure of the asymmetry of the probability distribution of a real-valued random variable. The skewness value can be positive or negative, or even undefined [4].

$$IQCS = \frac{(c-a)-(a-b)}{(c-a)+(a-b)}$$

Coefficient of Kurtosis

The degree of symmetry of particle size distribution may be defined by Coefficient of kurtosis.

$$Kurtosis = \frac{\sum\left(\frac{x-\bar{x}}{\sigma}\right)^4}{n} - 3$$

For a given frequency function kurtosis is a measure of how sharply the function peaks around the mode. Coefficient of kurtosis is a measure of kurtosis. Kurtosis is a measure of whether the data are peaked or flat relative to a normal distribution. That is, data sets with high kurtosis tend to have distinct peak near the mean, decline rather rapidly and have heavy tails. Data sets with low kurtosis tend to have a flat top near the mean rather than a sharp peak. For univariate data $Y_1, Y_2, \ldots$, YN, the formula for kurtosis is:

$$kurtosis = \frac{\sum_{i=1}^{N}(Yi-Y)^4}{(N-1)s^4}$$

Where Y is the mean, s is the standard deviation, and N is the number of data points.

The kurtosis for standard normal distribution is three. For this reason, some sources use the following definition of kurtosis:

$$kurtosis = \frac{\sum_{i=1}^{N}(Yi-Y)^4}{(N-1)s^4} - 3$$

This definition is used so that the standard normal distribution has a kurtosis of zero. In addition, with the second definition positive kurtosis indicates a 'peaked' distribution and negative kurtosis indicates a 'flat' distribution.

Skewness is a measure of symmetry, or more precisely, the lack of symmetry. A distribution, or data set, is symmetric if it looks the same to the left and right of the center point. For univariate data $Y_1, Y_2, \ldots, Y_N$, the formula for skewness is:

$$skewness = \frac{\sum_{i=1}^{N}(Yi-Y)^3}{(N-1)s^3}$$

Where Y is the mean, s is the standard deviation, and N is the number of data points.

The skewness for a normal distribution is zero and any symmetric data should have skewness near zero. Negative values for the skewness indicate data that are skewed left and positive values for the skewness indicate data that are skewed right. By skewed left, we mean that left tail is long relative to the right tail. Some measurements have a lower bound and are skewed right.

MATERIALS AND METHODS

The following powders were used as supplied indomethacin, folic acid, paracetamol and famotidine.

Particle Size Analysis

Sieve analysis:

A nest of BSS sieves were used. An accurately weighed quantity of test specimen was on the top (# 10, 16, 22, 44, 52, 60, 85, 100, 120, 200 and receiver) sieve and replaced the lid. The nest of sieves was agitated for 20 min. Each sieve was carefully removed from the nest without losing material. The weight of material retained on each sieve was used for calculation of various micromeritic parameters [5,6].

Microscopic analysis:

Particle size analysis was carried out by microscopic technique using calibrated ocular micrometer. Around 500 particles were counted avoiding aggregates and the obtained data was plotted as frequency distribution curve and cumulative frequency distribution curve [5,6].

Representation of Particle Size Distribution

The data obtained from all the experimentations were plotted as frequency distribution curve (percentage frequency versus mean particle diameter) and cumulative frequency distribution curve (cumulative percentage frequency versus mean particle diameter).

Calculation of IQCS and β_2:

IQCS was calculated by using the equation, $IQCS = \frac{(c-a)-(a-b)}{(c-a)+(a-b)}$, Where a = median diameter, b = lower quartile point and c = upper quartile point in a cumulative frequency distribution curve. $\beta_2 = \frac{\sum\left(\frac{x-\bar{x}}{\sigma}\right)^4}{n} - 3$

Where, x is the observation, x- mean, σ- standard deviation [4].

Effect of Process Parameters

Microspheres:

1% w/v of sodium alginate dispersion was prepared by dispersing required quantity of sodium alginate in specified quantity of distilled water [7,8]. 1 g Indomethacin was dispersed in sodium alginate dispersion and stirred to obtain homogenous dispersion with variable dispersion speed and dispersion time (F1: 1000 rpm, 3 h, F2: 1000 rpm, 4 h, F3: 500 rpm, 3 h and F4: 500 rpm, 4 h). Indomethacin dispersion was added slowly drop by drop with the help of 10 mL syringe (0.7 × 32 mm needle) into 1% w/v calcium chloride solution, which results in the formation of microspheres. The microspheres thus obtained were air dried for 24 h, followed by drying at 50°C.

Niosomes:

Different folic acid niosomal formulations were prepared by lipid film hydration technique. Accurately weighted quantities of surfactant (Span 60) and cholesterol in equal ratios, viz. N1-0.5:0.5, N2-1:1, N3-1.5:1.5, N4-2:2, N5-2.5:2.5 and N6-3:3 dissolved in 10 mL of diethyl ether in a round bottom flask. The solvent mixture was evaporated in a rotary flash evaporator under a vacuum of 20 inches of Hg at a temperature of 25 ± 2°C and the flask rotated at 100 rpm until a smooth, dry lipid film was obtained. The film was hydrated with 10 mL of buffer solution containing 1g of folic acid for 20 minutes at 40°C to 50°C with gentle shaking on a water bath. The suspension was maintained at room temperature for 2 h for the formation of Niosomes [9,10].

Solid dispersions:

500 mg of paracetamol and carrier i.e. urea and sorbitol were weighed in proportions of S1-1:0.5, S2-1:1, S3-1:1.5, S4-1:2. The mixture of paracetamol and carrier was taken in alcohol in a china dish and heated quickly with constant stirring on a water bath until it is melted. The melt was quickly solidified by pouring it on a tile, further by placing the tile on an ice bath. The resultant solid dispersion was stored in a desiccator till it is used [11,12].

Polymorphs:

Famotidine (1 g) was dissolved in 10 ml of (P1-Methanol, P2-1 % w/v PVP, P3-1 % w/v Tween 80, P4-1 % w/v PEG 4000) at 70ºC. The solution was kept at room temperature until it reached room temperature. Then the cooled solution was kept in a refrigerator (+8ºC) for a period of 24 hours. The precipitated crystals were spread on a petridish and air dried at room temperature. Then the dried crystals were stored in a desiccator for further use [13,14].

The prepared dosage forms and pharmaceutical powders were subjected to *in vitro* dissolution studies and were compared with IQCS and β_2 values.

RESULTS AND DISCUSSION

Sieving, as a method for size classification is widely used for characterizing the range of grain size present in powder. In this technique a quantity of powder is separated into fractions on a surface containing holes of uniform size. Stastical characterization of the particle size distribution data is one important tool that can account in variation

in aperture sizes. Thus in present report, four dosage forms were prepared with variable process parameters during preparation and were subjected to particle size analysis to get the particle size distribution data.

For symmetrical normal size distribution the peak frequency value, known as its mode separates the frequency distribution curve into two identical halves. But in case of asymmetrical particle size distribution, frequency distribution curve is skewed either positively or negatively depending on the proportion of particles present in the powder. If larger portion of fine particles is present positively skewed distribution curve is obtained. The significance of plotting percentage cumulative frequency distribution curve is that is possible to compare two or more particle population. A bell shaped frequency distribution curve is obtained when the particles are normally distributed. Quantitative stastical analysis of the data was done to get the values of IQCS and β_2 and results obtained are summarized in table. All the dosage forms confirmed asymmetric particle size distribution as their values were obtained to be either greater than or lesser than zero.

In the present study, various dosage forms (polymorphs, niosomes, microspheres and solid dispersions) were prepared altering their process parameters. The IQCS and coefficient of kurtosis values of all formulations were compared with their *in vitro* evaluation tests (Table 1).

Table 1: Parameters for *in vitro* dissolution studies for the dosage forms

Parameter	Microspheres	Niosomes	Solid dispersions	Polymorphs
Dissolution medium	pH 7.2 phosphate buffer	pH 7.4 phosphate buffer	pH 7.4 phosphate buffer	pH 2.5 acetate buffer
Volume of medium	900 ml	100 ml	900 ml	900 ml
Temperature of medium	37 ± 1°C	37 ± 1°C	37 ± 1°C	37 ± 1°C
Paddle rotating speed	50 rpm	100 rpm	100 rpm	50 rpm
Sampling interval	0.25 , 0.5 , 0.75, 1 and for every hour upto 12 hr	1 ml for every one hr upto 12 hrs	0 min, 10, 20, 30, 40, 50 and 60 min	0, 5, 10, 15, 20, 25, 30, 40, 50 and 60 min
Detecting wavelength	318.6 nm	280 nm	249 nm	265 nm

In case of microsphere, with increase in dispersion time and dispersion rate the release of drug increased. Order of release (Figure 1): F2 > F1> F4 > F3

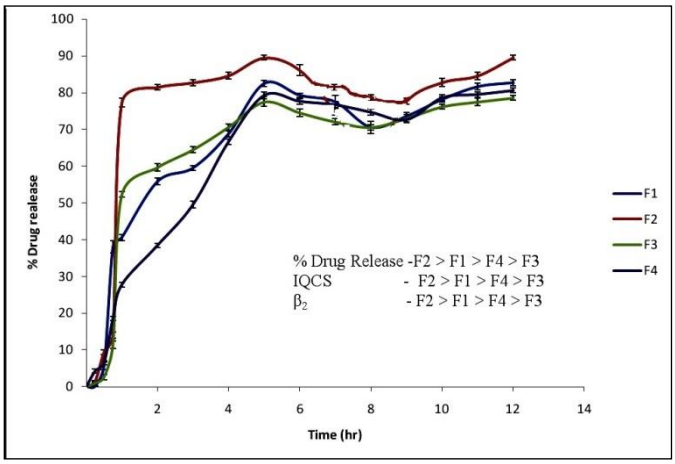

Figure 1: Cumulative percentage of drug release from microspheres

IQCS and β_2 values also increased in the way as the drug release. All the formulations were extremely skewed to the right and a platykurtic distribution was observed. With the increase in dispersion time and rate asymmetry increased and the percentage cumulative frequency distribution curve flattened [15]. For IQCS and β_2 values a positive correlation was found and on subjecting to linear regression between IQCS and β_2 with r^2 value 0.9995 (Table 2). Hence for the formulations with greater asymmetry and IQCS and β_2 value the percentage drug release was found to be more.

Table 2: Comparative statistical parameters of indomethacin microspheres based on particle size distribution data obtained on sieve analysis and optical microscopy

Formulation code	Avg. particle size	IQCS	B_2	Correlation Coefficient
F1	1.803 ± 0.024	1.437	0.021	0.9995
F2	1.326 ± 0.024	1.441	0.049	
F3	1.179 ± 0.135	1.161	-0.567	
F4	0.730 ± 0.018	1.268	-0.325	

In case of niosomes which were prepared using cholesterol and span 60, where the concentrations of span 60 was changed. The percentage drug release (Figure 2) of formulation 2 (1:1) was found to be greater than others.

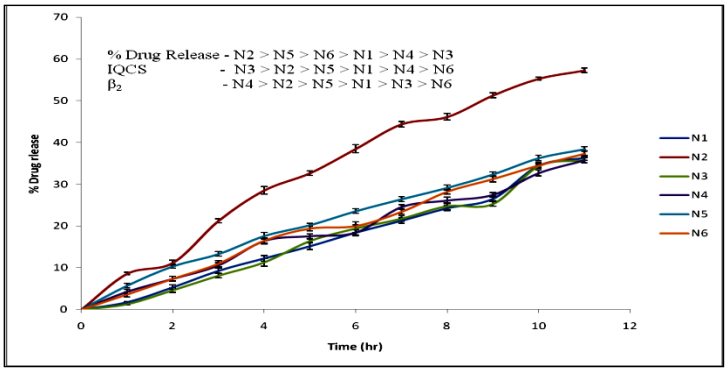

Figure 2: Cumulative percentage of drug release from niosomes

The distribution curve for all formulations was asymmetric, platykurtic and moderately right skewed. A positive correlation was found for IQCS and β_2 values with linear regression value r^2 0.076 (Table 3).

Table 3: Comparative statistical parameters of folic acid niosomes based on particle size distribution data obtained on sieve analysis and optical microscopy

Formulation code	Avg. particle size	IQCS	β_2	Correlation Coefficient
N1	3.323 ± 0.029	0.417	-1.93	0.076
N2	4.646 ± 0.054	0.514	-1.929	
N3	5.056 ± 0.065	0.565	-1.94	
N4	5.166 ± 0.045	0.499	-1.896	
N5	4.289 ± 0.091	0.316	-1.92	
N6	5.736 ± 0.064	0.531	-2.04	

Then solid dispersions were prepared by altering the ratios of polymers. The percentage drug release of formulation increased gradually as the ratio of polymer released (Figure 3): S4 > S2> S3> S1

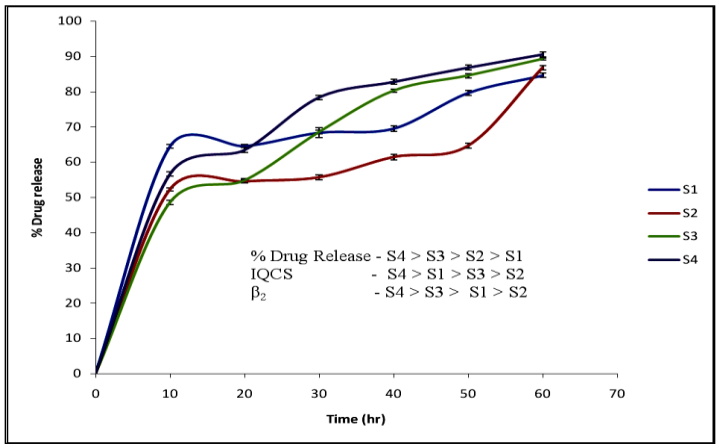

Figure 3: Cumulative percentage of drug release from solid dispersions

The β_2 values and IQCS value did not change accordingly as percentage drug release. Asymmetry was observed for all the formulations and moderately right skewed while formulation 4 was extremely right skewed; platykurtic

distribution was observed [16]. The number of fine particles was more in formulation 4 when compared to others. Therefore with increase in ratio of polymer the percentage drug release increases along with IQCS and β_2. On subjecting the IQCS and β_2 values to correlation and linear regression, a positive correlation was found with r^2 value 0.999 (Table 4). S4 was more asymmetric and no relation was found between ratio of polymer and the curve flattening.

Table 4: Comparative statistical parameters of paracetamol solid dispersions based on particle size distribution data obtained on sieve analysis and optical microscopy

Formulation code	Avg. particle size	IQCS	β_2	Correlation Coefficient
S1	2.341 ± 0.060	0.896	-1.351	0.999
S2	2.373 ± 0.026	0.205	-2.208	
S3	0.939 ± 0.014	0.767	-1.519	
S4	0.690 ± 0.006	1.084	-0.556	

While in polymorphs, where polymorphs were prepared by altering the solvents the percentage drug release in *in vitro* release was found to be like this (Figure 4), P2> P1 > P4 > P3. With the change in solvent used in the preparation of polymorphs the values of IQCS and β_2 did not change accordingly a random variation was observed. However, an extremely right skewed distribution frequency curve was observed.

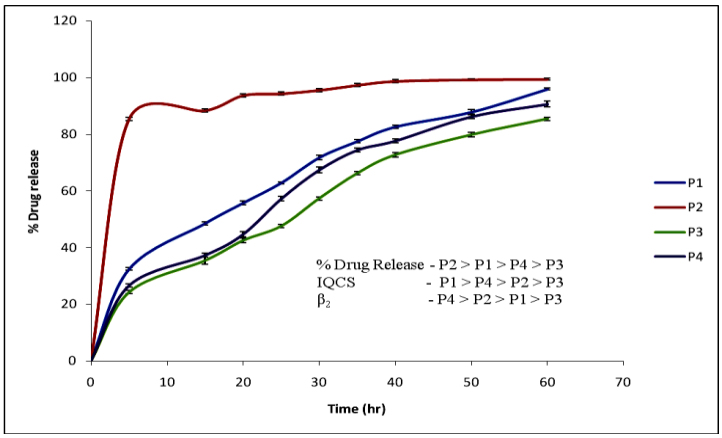

Figure 4: Cumulative percentage of drug release from polymorphs

A leptokurtic distribution was observed apart from polymorphs of Tween 80 which showed a platykurtic distribution. A poorly but positive correlation was obtained for IQCS and β_2 and when subjected to linear regression the value was found to be 0.068 (Table 5). The distribution curve for polymorphs of Tween 80 was found to be closer to normal distribution and asymmetry increased for polymorphs of PEG 4000.

Table 5: Comparative statistical parameters of famotidine polymorphs based on particle size distribution data obtained on sieve analysis and optical microscopy

Formulation code	Avg. particle size	IQCS	β_2	Correlation Coefficient
P1	0.096 ± 0.002	2.098	3.228	0.068
P2	0.185 ±0.006	2.188	4.761	
P3	0.223 ±0.010	1.313	0.12	
P4	0.132 ± 0.004	2.227	4.92	

CONCLUSION

The IQCS and β_2 values of the dosage forms are demonstrated. All dosage forms (microspheres, Niosomes, solid dispersions and polymorphs) showed positive correlation. Variation in process parameters showed an alteration and increase in asymmetry accordingly. By developing correlation between both the statistical parameters i.e. IQCS and β_2 provides an additional confirmation about the particle size distribution .Thus, establishing a correlation between

the two statistical parameters may be used as an additional parameter to quantitate the particle size distribution data of given dosage forms and may serve as a useful tool for pharmaceutical processing.

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