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PARTICLE SHAPE DESCRIPTORS AND ANGLE OF REPOSE OF A BIMODAL DISTRIBUTION SAMPLE

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Abstract

Particle size and shape influence the production of solid dosage forms. This study aimed to use the three shape descriptors available in the literature to describe the shapes of six compounds, and evaluate whether angle of repose might predict the flowability of a powder sample the same as those made by compressibility index and Hausner ratio. Images of cephalexin monohydrate, niacin, nystatin, sodium chloride, rifampin, triclosan were taken by a Raman Microscopy. Since the existing particle shape system could not characterize all six compounds, a new system is proposed. The powders of Rifampin and hydralazine hydrochloride were found to possess bimodal distribution during the study. Compressibility index and Hausner ratio predicted rifampin as poorly flowable, and predicted hydralazine hydrochloride as fairly flowable. But when either powder was poured through a test funnel, a dome formed in the middle of the horizontal base instead of the expected cone-like pile. This led to the question as to how the angles of repose should be measured. Our suggestion is that the angle of repose of a bimodal particle distribution powder be considered from the dome base in addition to the traditional approach, from the horizontal base, to avoid false prediction of flowability.

Key words: Bimodal particle distribution, flowability, hydralazine hydrochloride, Rifampin.

1. Introduction

Particle shape is an intractable factor in powder technology, because the surface of pharmaceutical solids abounds in asperities and rarely smooth. Even the same generation method for the same material may result in different particle shape. Particle shape may affect the flow properties of a powder by changing interparticulate and/or frictional forces

between the particles. Angular materials lead to a greater variation than more rounded materials in tablet compression [1]. Therefore, it may be necessary to change processing conditions in order to optimize a process.

The objectives of this study were three fold. First, the shapes of cephalexin monohydrate, triclosan, niacin, nystatin, sodium chloride, and rifampin were to be studied by Raman optical microscopy. Second, using their shapes to compare which one out of the three shape characterization system existing in the literature might describe these compounds. Third, can the traditional angles of repose designed to measure the particle population demonstrating Gaussian distribution be used for powder samples possess bimodal distribution? If no, is there a better way to take measurements?

2. Materials and Methods

2.1. Materials

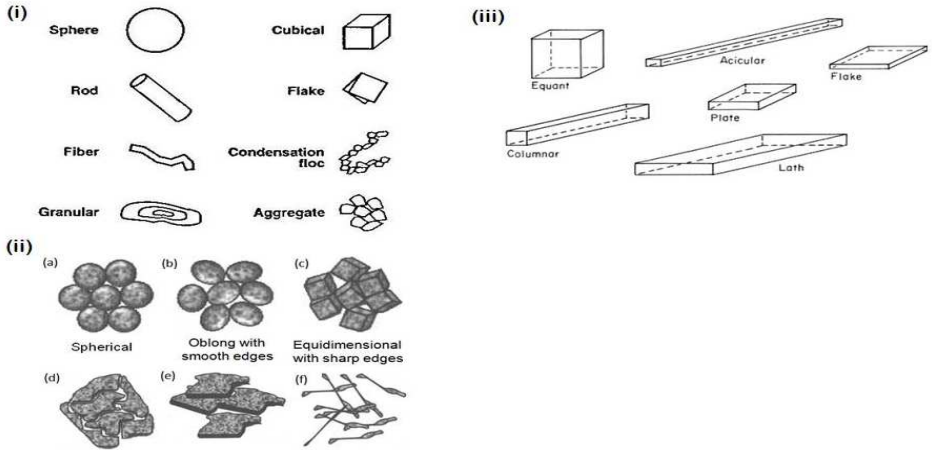
Cephalexin Monohydrate BP, USP (MP Biomedicals, LLC, lot 3370H) were purchased from VWR (Bridgeport, NJ), Hydralazine hydrochloride (HCl, lot 055K1703) was from Sigma-Aldrich (St. Louis, MO). Triclosan USP, Niacin USP, Nystatin USP, sodium chloride, and Rifampin USP were ordered from PCCA (Houston, TX).

2.2. Methods

2.2.1. Particle Shapes

Images of cephalexin monohydrate, triclosan, niacin, nystatin, sodium chloride, and rifampin were taken by optical microscopy (RamanRxn System Model # RXN1-785, Kaiser Optical Systems, Inc., Ann Arbor, MI). Their shapes were categorized using the three particle shape characterization systems in the literature. They are the systems defined by CS Randall [2], RJ Lantz [3], and USP-NF 2011 [4] (Figure 1).

Figure-1: Shape characterization system defined by (a) CS Randall [2], (b) RJ Lantz [3], (c) USP-NF 2012 [4].



2.2.2. Particle Size Distributions and Flowability.

(1) ***Sieving***

The sieve sizes chosen for the study were U.S Sieve numbers 70, 100, 120, 140, 230, 270, 500. Five grams of each study compound were sieved through the sieves in series starting from the sieve size 70 to sieve size 500 at the end. The sieves were then shaken for 100 times and the amount of sample retained on each sieve was weighed. The percentage compound retained on each sieve was then calculated.

(2) Angle of repose

In order to compare whether the flowability was predicted the same by angle of repose (peak height to peak base), compressibility index and Hausner ratio as listed in the USP-NF 2012 (Table 1) [4], five grams of a study compound was measured. When the powder was poured through a test funnel onto a chart of a sixteen-division circle, a conical pile formed. The internal angle between the surface of the pile and the horizontal surface was calculated as the angle of repose by the equation listed in the compendium [4].

$$\text{Angle of repose} = \tan^{-1}(2h/d) \text{----Eq. 1}$$

Where h is the height of the pile of drug from the peak to the ground;

d is the horizontal distance from the middle of the pile to the edge.

The same study was carried out for many compounds including rifampin and hydralazine HCl.

Table-1: Relationship of powder flowability with angle of repose, compressibility index and Hausner ratio listed in USP-NF 2012 [4]**.**

Flow Property	Angle of Repose (in Degrees)	Compressibility Index (%)	Hausner Ratio
Excellent	25- 30	< 10	1.00 - 1.11
Good	31 - 35	11-15	1.12- 1.18
Fair – Aid not needed	36 - 40	16-20	1.19 - 1.25
Passable- May hang up	41 - 45	21-25	1.26 - 1.34
Poor- Must agitate, vibrate	46 - 55	26-31	1.35 - 1.45

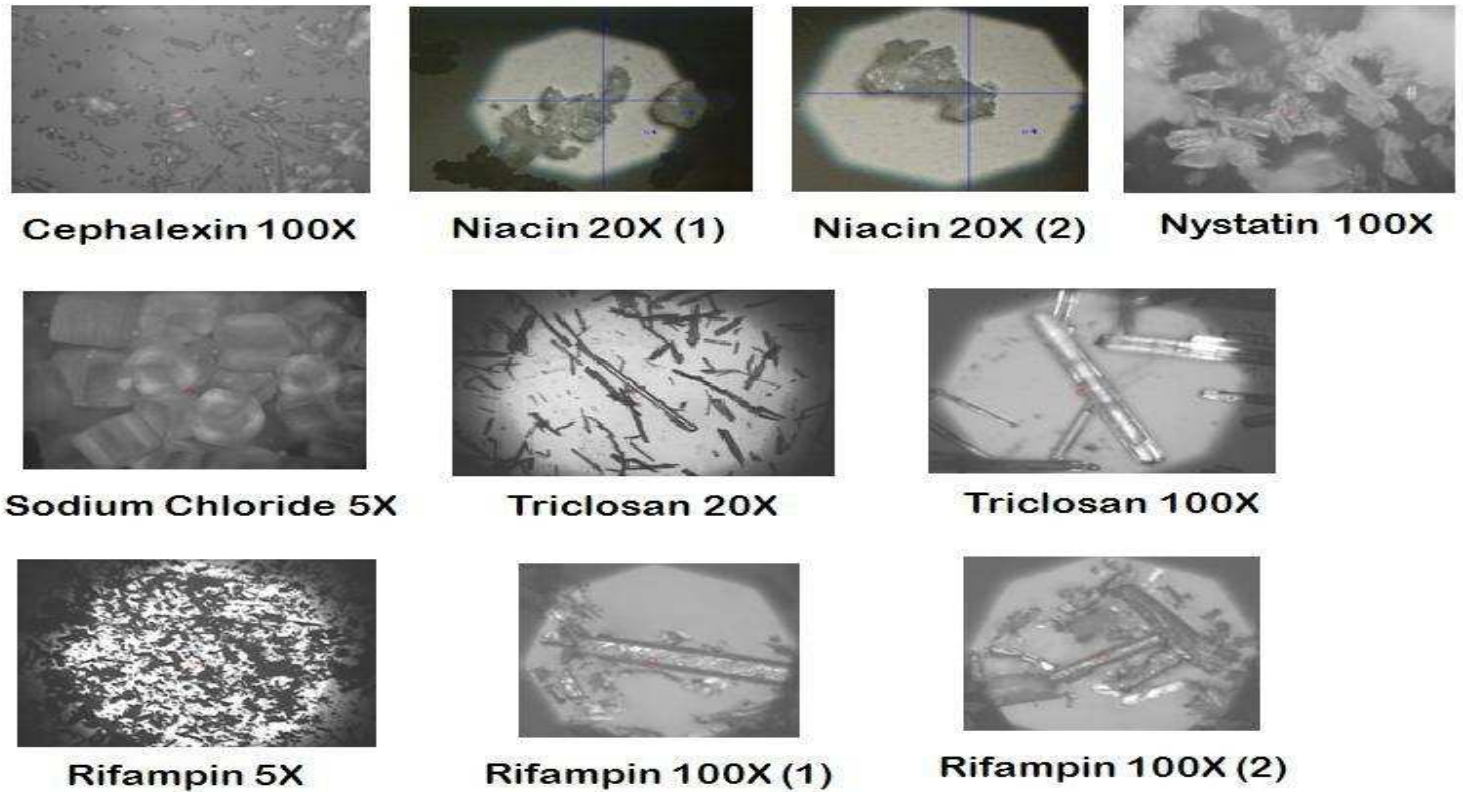
Very poor	56 - 65	32-37	1.46 - 1.59
Very, very poor	> 66	> 38	> 1.60

3. Results

3.1. Particle Shape Analysis

Images of the six study compounds, celpahexin, triclosan, niacin, nystatin, sodium chloride and rifampin taken by Raman Microscope were illustrated (Figure 2). Our Raman Microscope was equipped with lenses of three magnification power, 5X, 20X and 100X. The flake shape image of cephalexin was taken by 100X. The rod shape of triclosan article was most clear at 100X, although 20X was also included (Figure 2). Niacin powder was clear enough under 20X to demonstrate the interlocking nature of the particles, while the flake images of nystatin presented by Hologram software were better using a 100X lens. However, 5X lens was sufficient for taking the image of sodium chloride. Its cubic shape was clearly seen on the Hologram software. Under 100X, rifampin exhibited columnar shape by in two distinguished lengths (Figure 2).

Figure-2: Raman images of six studied compounds with appropriate magnifications.

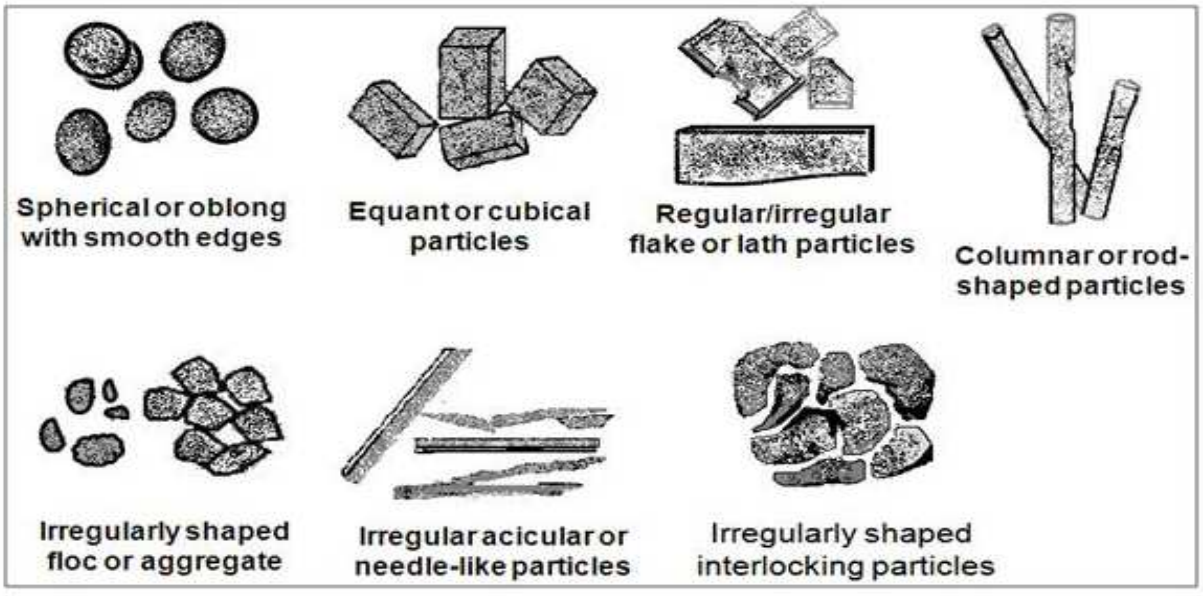


Among the six compounds tested, the system defined by CS Randall (Figure 1(i)) [2] was able to describe four shapes (the third column of Table 2 from the left), RJ Lantz system (Figure 1(ii)) [3] described two (the fourth column of Table 2 from the left), and USP-NF 2012 (Figure 1(iii)) [4] may describe four shapes (the second column of Table 2 from the right). We thus proposed a new descriptor system evolved from these three (Figure 3).

Table-2: Comparison of the three existing particle shape characterization systems by the shapes of six study compounds.

Compound	Magnification	Randall	RJ Lantz	USP NF2011	Our proposal
Cephalexin Monohydrate	100X	Aggregate	None	None	Irregularly shaped flake
Niacin	20X	Aggregate	Irregularly shaped interlocking	None	Irregularly shaped interlocking
Nystatin	100X	None	None	Acicular	Flake
Rifampin	20X	None	None	Columnar	Columnar
Sodium Chloride	5 X	Cubical	Equidimensional with sharp edges	Equant	Cubical
Triclosan	20X	Rod	None	Acicular	Rod

Figure-3: **Our proposed particle shape system, modified from those defined by Randall [2], Lantz [3] and USP-NF 2012 [4].**



3.2. Particle Size Distributions and Flowability of Rifampin

Rifampin possessed a bimodal distribution with sieve apertures of 125 and 25 microns as the two top frequencies (Figure 4a). Using the compressibility index and Hausner ratio listed in the USP-NF 2012 [4], rifampin was predicted as poorly flowable (30.2%±0.8% and 1.43±0.03, n = 3, Table 3). But when the powder was poured through a test funnel, a dome formed in the middle of the horizontal base instead of the expected cone-like pile (Fig. 5a). The angles of repose determined by the conventional approach differed from those computed from the pile height to dome base ratio (28.1^o±3.3^o versus 37.8^o±3.1^o, n = 3, Table 3). Hydralazine HCl also possessed a bimodal distribution with sieve apertures of 63 and 25 microns as the two top frequencies (Fig 4b). But niacin USP powder displayed as normal (Gaussian) distribution (Figure 4c). Using the compressibility index and Hausner ratio listed in the USP-NF 2012 [4] Hydralazine HCl was predicted as fairly flowable (17.9%±0.7% and 1.22±0.01, n = 3, Table 3), but again when the powder was poured through a test funnel, a dome formed in the middle of the horizontal base (Figure 5b) just like rifampin (Figure 5a). The angles of repose determined by the conventional approach again differed from those computed from the pile height to the dome base ratio (29.1^o±0.7^o versus 38.8^o±0.9^o, n = 3, Table 3).

Table-3: The angles of repose measured by the traditional method (peak height to horizontal base) and by our proposed method (peak height to dome base) to predict the flowability of rifampin and hydralazine HCl which were further compared with those made by compressibility index and Hausner ratio.

	Angle of Repose		Compressibility Index	Hausner Ratio
	Conventional	Measured from Dome		
(a) Rifampin				
Mean±SD	28.1±3.3	37.8±3.1	30.2±0.8%	1.43±0.03
Flowability	Excellent	Fair	Poor	Poor
(b) Hydralazine HCl				
Mean±SD	29.1±0.7	38.8±0.9	17.9±0.7%	1.22±0.01
Flowability	Excellent	Fair	Fair	Fair

After a chart of a sixteen-division circle was created on a colored paper, five grams of a variety of powders were poured through a test funnel in order to measure the angle of repose for each compound. The photos of the most two representative chemicals, rifampin and hydralazine HCl which possess bimodal particle distribution (Figures 5a and 5b). The photo of Niacin USP was also included (Figure 5c) as the reference which does not form an obvious dome

within the powder pile. The measurement of angles of repose for each was followed by taking the peak height to peak base according to the USP-NF 2012 [4] and taking the peak height to dome base based on our proposal.

Figure-4: Bimodal distribution with two top frequencies: (a) Rifampin USP at the sieve apertures of 125 and 25 microns; (b) Hydralazine HCl at 63 and 25 microns; (C) cumulated percent of distribution of Rifampin and Niacin.

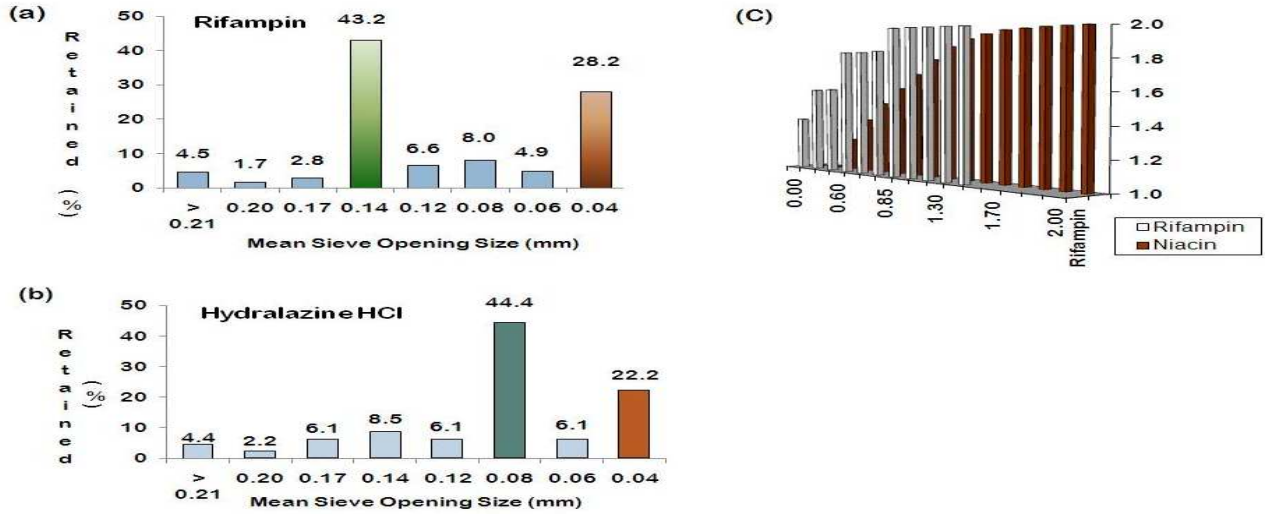
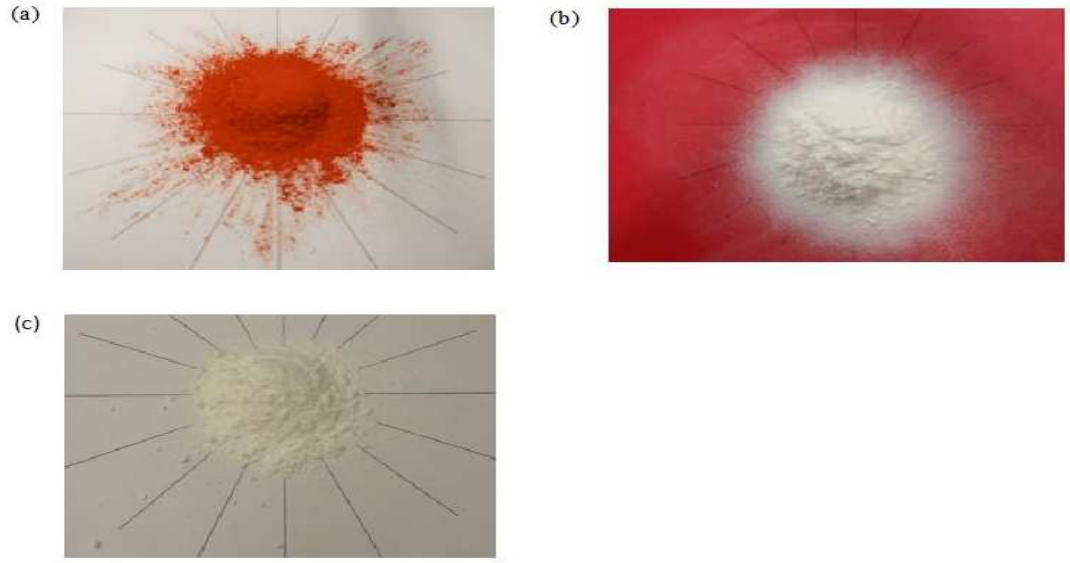


Figure-5: Free falls of three powders onto a chart of a sixteen-division circle through a test funnel for the measurement of angles of repose: (a) Rifampin USP, (b) Hydralazine HCl, and (c) Niacin USP (niacin served as the reference).



4. Discussion

Particle size and shape are important physicochemical parameters primarily due to their effects on the processing of the drug substance. They are determinants for polymorphic transformation, stickiness and flowability. They also affect drug stability due to the exposure of oxygen, light, and humidity [5]. Angle of repose has been used as an index of interparticulate friction or resistance to movement between particles.

5. Conclusion

The compendium particle shape system in the literature is for describing the shape of a single particle after being crystallized. Unfortunately, the process materials will generally not undergo such a step prior to being used in formulation. The Randall particle system is used to describe a single particle or cluster. The Lantz particle system is useful in describing clusters. None of the three existing particle shape systems is nearly perfect due to the drawing and the terminology labeled with each category. Additionally, many powder particles are not present in typical geometric patterns and sharp edges as the USP-NF system describes. Our proposed shape system contains seven groupings and the description in the system defines even more shapes. Based on our proposed method for measuring the angle of repose for bimodal distribution samples, flowability of rifampin and hydralazine HCl, is closer to those predicted by compressibility index and Hausner ratio. Due to the fact that the percentage of each modal distribution of a bimodal sample may vary, when the angle of repose is taken, both the values obtained from traditional method (from the horizontal base) and our proposed method (from the dome base) should be considered.

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