Effects of particle sizes on lactose diluents

ASSIGN BUSTER

Powder size and flow properties are crucial in dictating the quality of manufactured capsules in terms of weight variation and content uniformity. The aim of this experiment was therefore:

To assess and investigate the effects of different particle sizes of lactose diluents on their flowability which was measured by the angle of repose and percentage compressibility of the coarse and the fine lactose diluents and how this in turn affected the uniformity of weight and content of hard gelatine capsules that were made from the paracetamol and lactose powder mix.

The aim of the second part of the experiment was to assess particle size distribution of granulated sucrose (using statistical and graphing techniques) after two comminution methods namely kitchen mill and mortar and pestle and the sizing techniques used to determine the particle size distribution were sieve analysis, (and for the fines) microscopy and laser diffraction.

RESULTS:

EFFECT OF LACTOSE DILUENT PARTICLE SIZE ON CAPSULE MANUFACTURE:

Flow properties of lactose diluents assessed by:

ANGLE OF REPOSE:

Diluent Type: Coarse Lactose

Mean Angle of Repose (degrees): 41. 9

Standard Deviation (degrees): 1. 28

% Coefficient of variation (%CV): 3. 05

Diluent Type: Fine Lactose

Mean Angle of Repose (degrees): 53. 3

Standard Deviation (degrees): 6. 51

% Coefficient of variation (%CV): 5. 83

Fine lactose diluent had a bigger mean angle of repose than the coarse diluents. It also had a bigger standard deviation as well as %CV. It was also observed that while the coarse lactose diluent flowed perfectly to form a cone every time, the fine lactose diluents flowed in chunks and was unable to form perfect cones (very irreproducible).

% COMPRESSIBILITY:

Diluent type: Coarse Lactose

Bulk Density (g/mL): 0. 72

Final Bulk Density (g/mL): 0. 79

% Compressibility: 9. 35

Diluent type: Fine Lactose

Bulk Density (g/mL): 0. 52

Final Bulk Density (g/mL): 0. 63

% Compressibility: 17. 50

The fine lactose diluent had a much bigger % compressibility (Carr’s Index) than the coarse lactose diluent.

Manufactured capsule assessment was determined by:

UNIFORMITY OF CAPSULE WEIGHT:

Diluent type: Coarse Lactose

Mean Capsule Weight (mg): 544. 99

Standard deviation (mg): 5. 93

% Coefficient of Variation (%CV): 1. 09

Diluent type: Fine Lactose

Mean Capsule Weight (mg): 520. 92

Standard deviation (mg): 20. 46

% Coefficient of Variation (%CV): 3. 93

When using the coarse lactose, the capsules had a higher mean weight than when using the fine lactose. The distribution of the data around the mean value however (as represented by standard deviation and %CV) is much smaller when using the coarse than the fine diluent.

UNFORMITY OF CAPSULE CONTENT:

Diluent type: Coarse Lactose

Mean Paracetamol Content (mg): 17. 22

Standard deviation (mg): 0. 70

% Coefficient of Variation (%CV): 4. 07

Diluent type: Fine Lactose

Mean Paracetamol Content (mg): 20. 13

Standard deviation (mg): 2. 37

% Coefficient of Variation (%CV): 11. 79

When using the coarse lactose, the mean paracetamol content was lower than when using the fine lactose (and further away from the expected value of 20 mg paracetamol). Coarse lactose also had a lower standard deviation and %CV than when using fine lactose.

COMMINUTION AND PARTICLE SIZE ANALYSIS OF SUCROSE GRANULES:

Comminution method: Mortar and pestle

Weight before grinding (g): 100. 015

Weight after grinding (g): 99. 81

Percentage loss (%): 0. 21

Comminution method: Kitchen Mill

Weight before grinding (g): 100. 019

Weight after grinding (g): 99. 28

Percentage loss (%): 0. 74

There was a higher percentage loss of sucrose when using the kitchen mill than when using the mortar and pestle.

(* Rest of the calculations, workings and comments shown on attached paper*)

DISCUSSION:

EFFECT OF PARTICLE SIZE OF LACTOSE DILUENT ON CAPSULE MAUFACTURE AND ASSESSMENT

Powders are an important component for the manufacture of different drug formulations which is why it is essential to understand and control the different properties of powder. Primary properties e. g. particle size is essential to ensure weight and content uniformity, flow and mixing.

Indirect methods of measuring powder flow are angle of repose and %compressibility. Data obtained shows the CLD having a smaller mean angle of repose (41. 9o) than the FLD (53. 3o). This is because the drag forces of adhesion and cohesion between coarse particles is smaller than the driving force of gravitational pull due to particle mass on them. Fine particles conversely have high surface area that increases interparticulate cohesive forces causing particle aggregation resulting in poor powder flow. It is also seen that the CLD had a smaller Ïƒ(1. 28o) and %CV(3. 05%) than the FLD with Ïƒ(6. 51o)and %CV(5. 83%). This shows that because CLD had better and more uniform flow, results were more reproducible and constant. The FLD had poor, inconsistent flow producing irregular cones everytime. This led to higher deviation around the mean value. Second method to measure powder

flow was %compressibility expressed as Carr’s index which “ is a direct measure of the potential powder arch/bridge strength and stability”. The CLD had a smaller Carr’s index (9. 35%) indicating small difference between the bulk and final density. This is because when coarse powder flows it doesn’t form alot of void pores and spaces and has an optimal packing geometry. FLD conversely, because of high cohesive forces clumped together and formed many void spaces that collapsed (high amount of shrinkage) after tapping giving high index of 17. 5%.

The flow properties of lactose diluents affect uniformity of weight and content of capsules because of the ease and consistency with which it flows into the die. The results for uniformity of weight show that the mean weight capsule when using CLD was higher (544. 99 gm) than mean weight when using FLD(520. 92gm). This indicates that when using CLD, more flowed into the capsule due to better flow properties. However the Ïƒ resulting from CLD(5. 93gm) was much lower than when using FLD Ïƒ(20. 46gm). This shows that CLD was very efficient in flowing into the capsule with uniformity which led to narrow distribution of capsule weights around the mean value. This is also concluded by observing the % CV for the same reasons. The flow of the powder into capsules also controls capsule content uniformity. Results show that the mean capsule content when using the FLD (20. 13 mg) was infact much closer to the wanted value 20mg of paracetamol than when using CLD which had mean value 17. 22 mg. This anomaly may have been due to improper mixing of the diluent with paracetamol. The FLD however had more inconsistency of content (due to poor, non-consistent flow) as depicted by its

higher Ïƒ(2. 37mg) and CV(11. 79%) than when using the CLD with Ïƒ(0. 7mg) and CV(4. 07%).

BP limits for uniformity of weight is ±7. 5% about the mean value. When calculated for coarse and fine diluents, all capsule weight values for both diluents were between the calculated ranges. Hence both CLD and FLD passed the BP limits of weight uniformity. The BP test for capsule content is ±15% of average content. The BP limits for uniformity of paracetamol content however is only ±5% of average content. When calculated for coarse and fine lactose diluents, it was determined that while all the paracetamol content when using the CLD were between the calculated range thereby passing the test, the content for 5 capsules when using the FLD lay outside the BP limits hence failing the test.

COMMUNUTION AND PARTICLE SIZE ANALYSIS

Different milling techniques are used depending on what properties are desired for the end product (particle size and amount of fines). From the two comminution methods used, it was determined by statistical means that the mean particle diameter using mortar and pestle (473. 7µm) was much bigger than that obtained from kitchen mill (159µm). The latter is therefore more effective in producing smaller particles. It’s worth mentioning however that powder obtained from mortar and pestle achieved normal distribution with smaller Ïƒ(284. 5µm) around mean. The powder obtained from kitchen mill had much wider distribution of particle sizes Ïƒ(431. 5µm) around mean value and didn’t follow normal distribution. This is because kitchen mill produced alot of fines hence size ranges from very small to big. The amount of fines produced also depends on comminution process used as clearly seen by the

2 methods. While kitchen mill produced fines constituting 25. 5% of total weight, mortar and pestle produced only 4% of fines. The kitchen mill therefore is more efficient in producing smaller, finer particles. It should be considered however that the particle size distribution is very much dependant on the milling time. The longer the milling time, the smaller the particles obtained. The kitchen mill had a higher %loss(0. 74%) than the mortar and pestle(0. 21%). This however can be minimised by exercising more care e. g. ensuring (with aid of a brush) that all the powder is removed from kitchen mill (and not stuck under the blades). Of the total energy put into a milling operation, only 2% goes into size reduction. So while kitchen mill had a uniform mechanical grinding of the powder because it was automated, the mortar and pestle was a manual process hence required more manual force in an attempt to uniformly grind the powder. It was determined by observing the %undersize (from sieve analysis) and relating it to BP description of powders, that powder obtained from mortar and pestle is classified as coarse powder because even though all the powder passed through 1400µm mesh, not more than 40% (24. 86%) passed through 355µm mesh. The powder obtained by kitchen mill is classified as intermediate between moderately fine and coarse. This is because more than 40% of powder (64. 5%) passed through 355µm mesh (lower limit for coarse powder) but more than 40% (50. 63%) passed through 180µ mesh (lower limit for moderately fine powder).

Apart from above two, other methods such as cutter mill, roller mill, hammer mill, vibration milling, ball mills and fluid energy milling can also be used for particle comminution.

Once powder has been grinded, it’s essential to measure particle sizes. From the three sizing techniques used, the most appropriate for measuring mean particle diameter of the total product from the milling process is sieve analysis since this was the only method that used all 100g of the powder. Microscopy and laser diffraction were only used to measure size distribution of the fines. It should be noted that although sieve analysis used all the powder, the uppermost and lowest sieve size, limits analysis of powder. For e. g. in this experiment particles Ë, 63µm and above 500µm couldn’t be analysed further. Another disadvantage of sieve analysis is that it’s rarely complete because some particles take a long time to orientate themselves to pass through the sieve mesh. Size distribution is therefore dependant on time of vibration during experiment.

The fines obtained from the comminution methods were analysed using microscopy and laser diffraction. One major disadvantage of light microscopy is that because it’s based on 2D images, particles are assumed to be randomly oriented in 3D. Although this assumption may be valid for spherical particles, it is very unlikely that non-spherical particles will orient themselves with their minimum dimensions in plane of measurement. This leads to over estimation of size as the largest dimension of particle will be observed. This reasoning probably explains why the mean particle size of the fines obtained from both comminution methods were much higher (30µm range) than that obtained from the laser diffraction (15µm).

Various factors influence the sizing technique used. While laser diffraction and sieve analysis only determine particle size distribution, microscopy takes into account particle shape also. Furthermore, while sieve analysis can only

be used for particles between 45-1000µm (ISO), light microscopy and laser diffraction can be used to analyse particles greater than 1µm. SEM and TEM however can further extend size limit to less than 1µm. Other factors such as cost, time (sieve analysis is much quicker as it can take large amount of sample) and efficiency can also influence the choice of method.

The experiment performed had many errors resulting in discrepancies between calculated and graphical mean diameters from the 3 sizing techniques as well as weight and content uniformity of capsules. The errors were random human errors such as graphing accuracy, incomplete transfer of material between apparatus, measurement/parallax errors etc that can only be minimised by exercising due care and performing experiment several times (or taking more sample) and then obtaining average. The %error obtained for microscopy and laser diffraction were also significant and these ware due to graphical errors of plotting and other values that were not considered (on the graph) but were accounted for in theoretical calculations.

CONCLUSION:

From the experiment, it can be concluded that CLD had better flow properties which in turn influenced the weight and content uniformity of capsules. This reinforces the concept that powder properties are crucial in dictating ease and efficiency of the whole manufacturing process. Furthermore, it can also be concluded that different comminution methods produce differing end product properties from the same starting material which is necessary to control in order to ensure that the desired performance of the formulation will be achieved. Different sizing techniques can be

employed to measure particle sizes all of which have their respective advantages and disadvantages.