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BETTER PARTICLE SIZE SOLUTIONS

Particle Sizing with Dry Dispersion Can Be the Best Choice for Pharmaceutical Analysis

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David Pugh has been involved in gas, liquid, surface area and particle size analysis for over 30 years. Currently, his main expertise is in particle size analysis of suspensions and dispersions, as well as dry analysis of numerous commercial products, especially in the pharmaceutical and biotechnology sectors.

Abstract

This paper looks at laser diffraction technology which when initially conceived only measured particle size by diluting a sample with a suitable diluent and pumped the mix through a sample measuring cell. It explains how the move away from using solvents encouraged the use of measuring sample dry rather than wet and explains what the barriers to dry measurement were and how they were overcome during a period of 25 years. Pharmaceutical powders are generally considered to be some of the most cohesive a particle scientist will come across and generally are very demanding when using the wet method. In this paper we will demonstrate how a modern dry laser diffraction is able to analyse these cohesive samples and achieve reliable repeatable results with an eco-friendlier method.

Keywords

Particle size distribution, laser diffraction, eco-friendly, Pressure titration curve, agglomeration, dispersion, zeta potential, API, obscuration triggering, enclosed sample cell, velocity bias, cohesive, co-axial eductors, crystalline particles, Micro-crystalline Cellulose, Sodium Starch Glycolate, Dextrin, Cetirizine Hydrochloride, Ticagrelor, Omeprazole, Flunarizine Hydrochloride, Magnesium Stearate, Amlodipine Besylate

Introduction

When laser light diffraction analysis was first introduced in 1974 to measure particle size faster, only wet dispersion was available. Dry sample analysis was introduced 1 year later in 1975 and although most products being measured were dry rather than in suspension, most applications were measured wet. Even cement in the early days was predominantly accurately measured in alcohol and inaccurately measured in water. Why was it the case that many samples were measured wet when a number of issues had to be overcome to get accurate repeatable results? Let us look at the issues laboratory technicians faced with samples that either dissolved or agglomerated in water.

In the first instance, they would need to find a solvent which would disperse the sample without any dissolution taking place. The problem was that many of these solvents were toxic and expensive to both purchase and dispose of afterwards ecologically. An example I am personally acquainted with is that of chocolate which was measured by dispersing it in Genklene (1,1,1 – Trichloroethane), followed by 30 seconds of ultrasound to complete the dispersion prior to analysis. The problem was Genklene,s toxicity, led it to being phased out for the safety of its users (Carcinogenic) and internationally by greenhouse emission protocols.

In the second instance where agglomeration of a sample was known or seen to take place when dispersed in water, the users had to find means with which to prevent agglomeration. Firstly, where predominantly fine material was evident on the surface of the dispersant, a suitable surfactant needed to be

found to reduce the surface tension and the choice was one of four surfactants (nonionic, anionic, cationic, or amphoteric). Secondly, there is the issue of fine particles agglomerating in the water, so a suitable admixture must be chosen to add to the water to prevent agglomeration. It is known that the zeta potential of a particle will change depending on the pH. For example, at pH 3 the zeta potential may be +30mV and at pH 10 the zeta potential may be -25mV so highly stable – so no agglomeration is to be expected at either pH, however at pH6 the zeta potential may be 0mV i.e., the isoelectric point where maximum agglomeration is likely to occur, and an oversized inaccurate result will ensue. With all these factors to take into account, it is not surprising that so many SOP,s used, either produce an erroneous result or differing results from different operators using the same standard operating procedure but interpreted in different ways.

The gradual change from wet to dry measurement.

Over the past 30 years, dry particle size analysis has become more prevalent especially in the pharmaceutical industry where previously exotic solvents were used to disperse the API in order to disperse but not dissolve the formulation. What has changed in that time? Industries such as minerals, cement and powdered coatings all originally measured wet but are now exclusively measuring their products dry for the last 30-40 years. The main reason for this is that these applications have always been relatively easy when measuring dry, even with the older dry powder feeder designs. It has only been with the gradual improvement of these designs, that other industries including pharmaceuticals, have been able to take advantage of a method which is faster, greener and as a result of using more sample, is more statistically correct.

Improvements in dry powder feeder design.

Feed Control

Let us have a look at the early designs and see what improvements have been made in order to provide a more accurate, repeatable result. Originally the sample was transported to the dispersing zone under gravity, by pouring the sample into a funnel at the bottom of which was the dispersion zone which was an area where a jet of air impacted the sample and dispersed it well enough to deliver to the measurement cell to provide a representative result – in theory. A primary flaw was that feeding the sample en masse was not a controlled feed and really only provided an answer for dry particle measurements where the sample was not cohesive. This tended to favour particles of a larger size containing little or no moisture and not the much finer and cohesive samples more typically produced within the pharmaceutical industry.

The next development was to deliver the sample on a vibratory chute to the sample funnel where it again fell under gravity to the dispersion zone. There were 2 issues with this method. The first is that material, particularly cohesive powders would vibrate down the chute in varying concentrations so you might either have too much material delivered to the disperser or not enough – feast or famine. If too much cohesive sample arrived at once then there was always the possibility that the air disperser in the early days was not efficient enough to disperse all of the sample in the fraction of a second that the sample was in intimate contact with the air. For cohesive powders, this could result in a fine dispersed distribution and a coarse undispersed population. In addition the process worker obtains a representative sample but all of it may not be used in the measurement. Some sample could be left on the vibratory tray and in addition to this, there were timing issues. When sample was vibrated down the vibratory tray, the measure command would only be activated when the operator deemed that there was a high enough sample concentration passing through the sample cell for it to be a valid measurement. Not only that, the run time was preset, so if the sample ran out early then you would only be measuring noise as the signal to noise ratio plummeted. Alternatively, if you had too much sample, then not all of it would be measured when the run time ran out.

Computer Software Control

This problem was eventually solved with the advances in computers and system software in the late 80,s early 90,s. A software filtering technique known as obscuration triggering was incorporated into the software. The operator could press measure/run at any time but no sample sweeps would be taken until there was a certain pre-set minimum obscuration achieved which would initiate the actual data taking without the operator needing to do anything more. Not only that, when the last of the sample was passing through the measurement zone and dropped below the pre-set

minimum obscuration level, the data collecting would stop and the measurement finished. The advantage of this is that at least 99% of the sample would have been measured with a very high signal to noise ratio, giving a high degree of confidence in the result. Even further confidence is gained by running the sample a number of times (typically 3) and producing a reassuring perfect overplot comparison of the 3 runs.

Hardware changes that work

In order to know what hardware changes were needed to improve the measurement, it is important to appreciate what the pre-requisites are for a successful dry analysis. There must be representative sampling and delivery of the sample to an air eductor which will disperse the sample. Further dispersion, involving mainly particle-particle shear will take place along a flow path consisting of a tube of constant diameter. This tube transports the dispersed sample to the measurement zone which should be an enclosed sample cell in order that no velocity biasing takes place.

This broad statement covers the following details which are a must, if we wish to analyse cohesive pharmaceutical powders accurately. There must be minimal/ideally zero cross contamination from sample to sample, so the feed tray must be as stick resistant and easy to clean as possible. All the sample presented to the tray must be transported and analysed. There must be adequate predispersion of the agglomerates and this should be confirmed by a pressure titration curve. In effect, the cohesive sample has to be dispersed but not milled. The sample flow path to the measurement cell must be of a constant inner diameter and the sample nozzle must be constructed in wear resistant materials. When the sample arrives at the measurement zone, which should be an enclosed cell, the largest and smallest particles should be travelling at the same speed, so both are equally represented in the data. Having a constant diameter flow path and a closed measurement cell are key to achieving zero velocity bias. If these hardware musts are not incorporated, there is always a danger of the result being artificially biased towards the fines for cohesive samples.

Hardware changes that failed

Some hardware changes that were incorporated failed to meet the criteria outlined above and most were rejected eventually by the laser diffraction companies that proposed them such as predispersion via rotating brushes. These brushes were used to predisperse the powder but this technique resulted in cross contamination of the sample from run to run as sample was caught up in the brushes potentially contaminating the next result. In addition having moving parts is bad from a maintenance perspective leading to a shorter mean time before failure.

Other hardware “improvements” though are still being used such as using a baffle type arrangement before the nozzle outlet. Cohesive fragile crystalline particles will fracture upon impingement as the sample laden air strikes the baffles. This baffle arrangement is totally unsuitable for pharmaceuticals (which are crystalline) as it produces a finer milled result rather than the real size which may please the laboratory technician but not necessarily the patient.

Using sieves under vibration, with ballbearings to predisperse the sample initially seems like a good idea. However when testing this “innovation” with cohesive materials, much of the sample sticks to the sieve and around the ballbearings thus never reaching the measurement zone. In addition there is usually sample build up on the chute and in the sample flow path rendering the result unrepresentative as much of the sample is unable to reach the measuring zone. Cleaning of the entire flow path for this system is absolutely necessary between pharmaceutical sample measurements to ensure the efficacy of the result. As fast, repeatable and accurate results are what is expected by the user rather than laborious cleaning, this is not the ideal system.

There are still dry dispersion units which mill the sample and then shoot it out of a nozzle whose inner diameter increases before being emitted into ambient air creating the adverse phenomenon of “velocity biasing”. It has already been recommended that every sample when measured dry should undergo a pressure titration analysis which involves measuring the sample at a minimum of 4 different pressures. Free flowing materials, such as sand and powdered coatings, will produce the same size result at all pressures when measured by a well designed dry powder feeder. However for cohesive samples such as pharmaceuticals a range of measurements at pressures typically from 0.5 - 4 Bar is absolutely necessary to determine what range of pressures will result in deagglomeration, what range of higher pressures will result in breakage and in between these 2 pressures lies the working pressure range which will disperse the sample without milling. This is

possible to do in a very short time frame with a well designed dry powder dispersing system. However, with a system that does not have a sample delivery tube of constant diameter and even worse, ejects the sample not into an enclosed air cell but into ambient air for a distance before the particles pass the laser, there are serious issues, the worst of which is velocity biasing.

What is velocity biasing?

The largest particles with the greatest momentum, shoot across the laser beam like bullets. The smaller particles are slowed down dramatically by surface drag from the ambient air. This results in the smaller particles taking longer to pass through the laser beam and thus being over-represented in the analysis compared to the larger particles. This results in a finer distribution which will give a false picture of the true particle size. The higher the pressure used to disperse the sample in this instance, the greater the difference in velocity and hence an even finer result. This is called velocity bias. These 2 design errors result in sample milling and a slowing down of the finer particles which will produce an undersized finer result. A big common mistake is to attribute the finer result to better dispersion, but the reality is a bad design can present a result to the user that although it looks good is not accurate. The acid test is to test the sample at different pressures and if you are not able to find a pressure range, where the same result can be achieved then the result has to be suspect. The other drawback to this technique, particularly for pharmaceutical active ingredients is the serious health and safety issue of having active ingredients in open air and not in a contained system.

Which type of eductor should be used?

The final area of improvement within dry powder feeders over the last 20 years is the increased use of co-axial eductors rather than traditional standard eductors. In the early days standard eductors were only used for dispersing particles which were not prone to breakage so the dispersion in the eductor was very aggressive. If however you wished to measure a more fragile material such as crystalline pharmaceutical powders then the standard eductor could not be used as it would mill the sample. It is for this reason that the less aggressive co-axial eductor was introduced which at certain pressure ranges could disperse without milling. The advantage of the co-axial eductor was that the sample path was straight with no 90 degree bends in the flow path and hence cohesive pharmaceuticals could be dispersed with only particle-particle shear and particle wall dispersion. With no 90 degree bend in the design there will be no milling of crystalline particles, giving a false undersized result. Bettersize has adopted all these improvements in its dry powder feeder design, and we will have a look at some pharmaceutical sample results measured on these dry systems to prove their validity.

Methods

The laser diffraction system chosen to measure the particle size distribution of Micro-crystalline Cellulose, Sodium Starch Glycolate, Dextrin, Cetirizine Hydrochloride, Ticagrelor, Omeprazole, Flunarizine Hydrochloride, Magnesium Stearate and Amlodipine Besylate was the Bettersizer 2600. This system is composed of an optical bench, a built-in dry dispersion system designed to comply with all the improvements made over the last 20 years (Feed control, sample flow path including a tube of constant diameter, use of co-axial eductor and an enclosed cell) a computer and printer. It uses a first principles technique called laser diffraction, which has been in use for 48 years. The reason for diffraction's wide usage from its early inception is due to the methods fast results, repeatability from user to user and, its resolution over such a wide particle size range.

How does laser diffraction work?

The original laser diffraction systems used the Fraunhofer theory. This theory assumes that all particles are opaque and spherical. In addition, when there is a particle / laser light interaction, it assumes that all the light scattered is diffracted light. There is no taking into account any refracted or reflected light from the particle. The Mie theory is a rigorous theory that describes the scattered light field, which is fit for use with most particles. However, large particles whose size is > 40x the wavelength of the laser (25 microns typically), the Mie scattering calculation is less needed and the Fraunhofer theory can be used instead.

When a laser beam interacts with a stream of particles passing through it, they will be irradiated, and a part of the light will be scattered from the original propagation direction. This is called laser light scattering or laser diffraction. The particle size affects the scattering

shape both in terms of light intensity and angle. The optical system consists of a laser beam from a semiconductor laser which passes through a wave filter, where it expands, and aligns into a parallel beam. The sample measurement cell is installed in the path of the laser beam, a forward photodetector is installed on the focal plane of the collimating lens to detect scattered light created by large particles at the forward angles, while lateral and backward photodetectors are placed for collection of scattered light signal caused by smaller and submicron particles. When the particle size is small it diffracts low levels of laser light at wider scattering angles however when the particle size is large, higher amounts of scattered light are created covering a smaller and narrower angular scattering range. The light signal is transformed into an electrical signal, which is then used in the inversion calculation based on Mie theory to provide a particle size distribution.

The Mie theory describes the quantitative relationship between the particle size, concentration, the diffraction angle, and the intensity of the scattered light. Based on this relationship, the laser diffraction particle size analyzer can be used for particle size distribution measurement.

Bettersize laser diffraction systems are well known for their reliability, accuracy and value for money. What is not known, as much, is their world beating dry powder feeders. They have the ability to out perform other systems in terms of ability to disperse cohesive materials such as many pharmaceuticals but without milling them.

There are many materials which can withstand high dispersion pressures without breaking or being abraded such as cement. There are other materials however which will deagglomerate with pressures greater than 0 Bar up to say 2 Bar and then not deagglomerate any further, maintaining their particle size distribution with increasing pressure up to 3 Bar. As part of the standard operating procedure (SOP), the working pressure would have to be the midway point in this working zone (2.5 Bar). We have examples of crystalline materials (such as many pharmaceuticals) that would be milled by standard eductors with increasing pressure but not milled when using a co-axial eductor. It is possible to make measurements from 1-4 bar pressure on some pharmaceutical ingredients without much change in the result. From this we can infer that many fragile or crystalline materials such as pharmaceutical products can be successfully analysed dry rather than wet with exotic solvents, with complete confidence in the results.

So the method to use when analysing pharmaceutical ingredients is to use a dry powder feeding system which feeds and analyses at least 99% of the sample. It is also important to note that the technician should use a dry powder feeder incorporating a co-axial eductor and a totally enclosed sample cell, so no velocity biasing takes place. In addition, a full pressure titration should be performed to determine which is the most appropriate working pressure range that should be used. There should be zero milling of the powder taking place in the sample flow path only deagglomeration and dispersion of the sample. To ensure that this is the case a typical pressure titration should be performed in either 0.5 Bar or 1 Bar increments from 0.5/1 to 4 Bar pressure in order to see the whole picture and then evaluate the most appropriate working conditions.

Each type of sample measured will produce its own specific titration curve. Samples have been tested which have produced their own titration fingerprint. The samples tested include active pharmaceutical ingredients (API) and non-active materials such as binders. The materials chosen for testing are Micro-crystalline Cellulose, Sodium Starch Glycolate, Dextrin, Cetirizine Hydrochloride, Ticagrelor, Omeprazole, Flunarizine Hydrochloride, Magnesium Stearate and Amlodipine Besylate. Some disperse easily and other samples when first presented to you are agglomerated to a high degree.

For those more static, agglomerated samples an easy way to pre-disperse them is to place the sample feed tray in a sieve pan. Then place a 500 or 625 micron sieve on top of sieve pan containing the feed tray, add the sample on top of the sieve and tap the sieve rim with a small solid metal object to create a momentary vibration. Within 30 seconds all the sample will have passed through the sieve, deagglomerated from balls to a much finer powder without any breakage taking place. This is a simple but effective pre-dispersion method. For larger free flowing powders this is not a necessary task. A vibration rate for the sample tray should be set which delivers the sample to the sample cell via the co-axial eductor in a controlled way – not too much, not too little. The obscuration monitor assists the user to determine the correct degree of vibration. The sample is measured this way 3 times at 4 different pressures at least ranging from 0.5-4 Bar.

Results

The first sample to be tested was **Micro-crystalline Cellulose (MCC)** which is a commonly used excipient in the pharmaceutical industry for binding the active pharmaceutical ingredient (API). It has excellent compressibility properties and is used in solid dose forms, such as tablets. Tablets can be formed that are hard, but dissolve quickly – essential if it is to be absorbed into the body releasing the active pharmaceutical ingredient easily. MCC is the most common cellulose-derived excipient used in the pharmaceutical industry (1).

As MCC is a free-flowing material, binders should be added to tablet formulations to add cohesiveness to powders thereby providing the necessary bonding (2). The MCC can be added directly to the sample feed tray ready for analysis. In Figure 1 we can see, results from all 4 pressures are very similar, so in order to find the specific working range for analysing this sample for the future, we need to look at the finer detail, for this reason we exported the key parameters to excel to produce a pressure titration curve.

In Figure 2 we can immediately see that the values for the d10, d50 and d90 are flat for 1 and 2 Bar but then between 2 and 4 Bar, there is a slight reduction in size. As the sample is large but crystalline, it is possible that some breakage of this crystalline material has taken place for the d10 and d50 values at pressures greater than 2 Bar. From this information we can deduce that the working pressure range for measuring this material is between 1 and 2 Bar. My preference would be to measure MCC at 1 Bar pressure and the d10 at this pressure is 15.77 microns, d50 is 55 microns and the d90 is 125.4 microns.

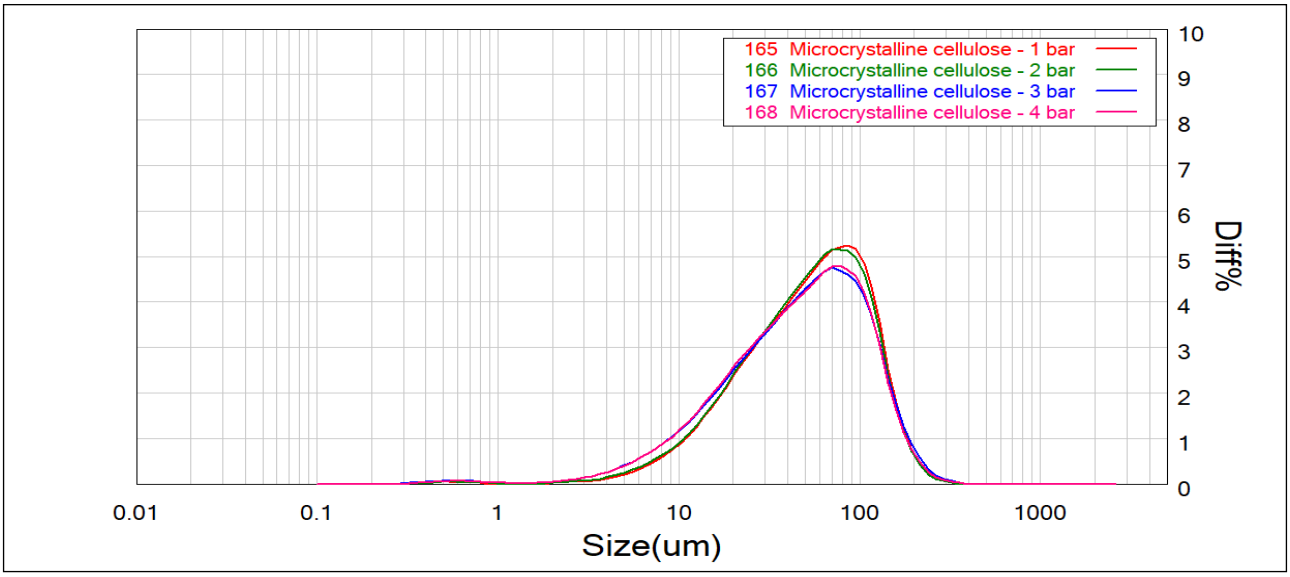


Figure 1. MCC particle size distribution from different pressures

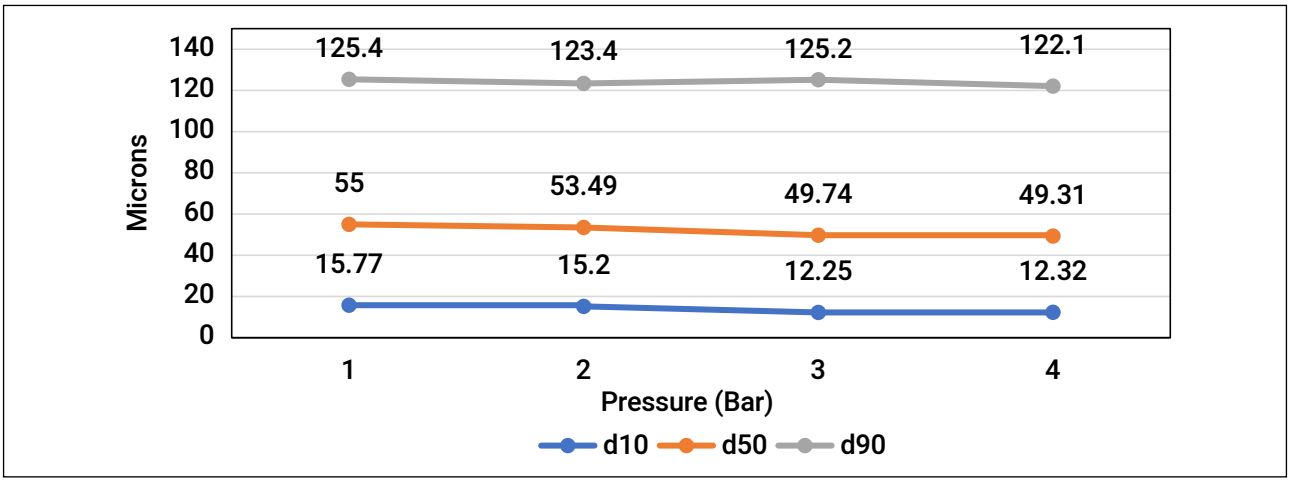


Figure 2. Values for the d10, d50 and d90 of MCC from different pressures

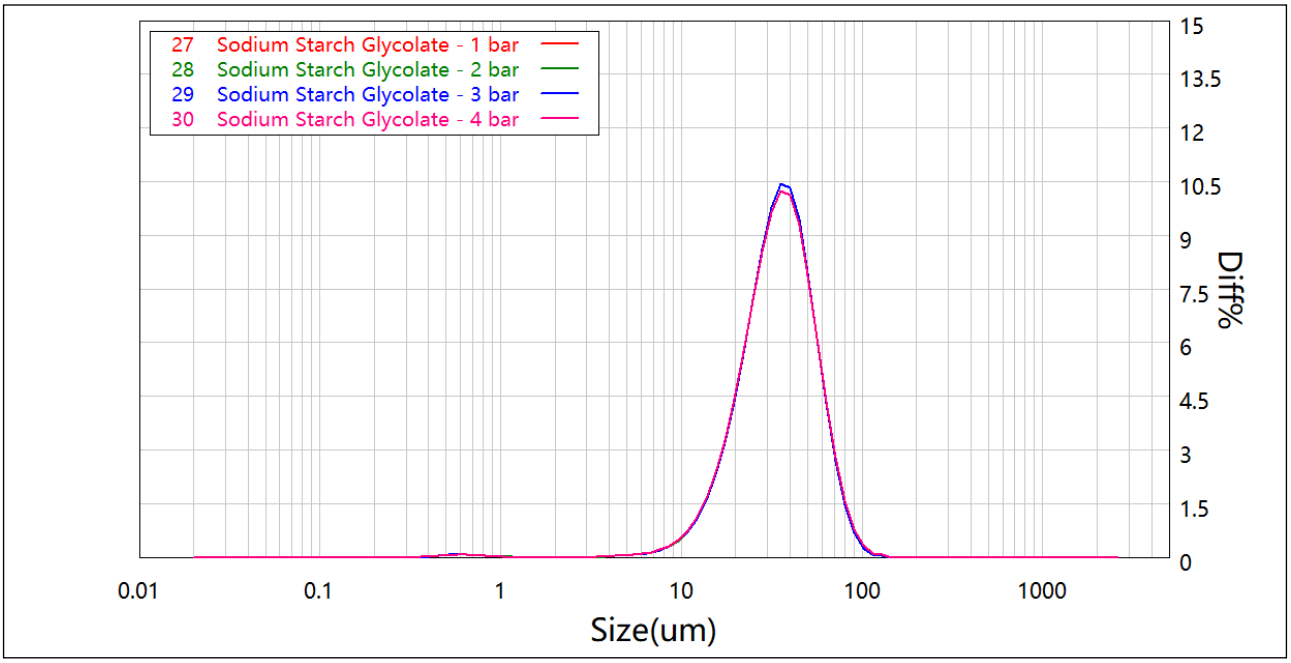


Figure 3. Sodium starch glycolate particle size distribution from different pressures

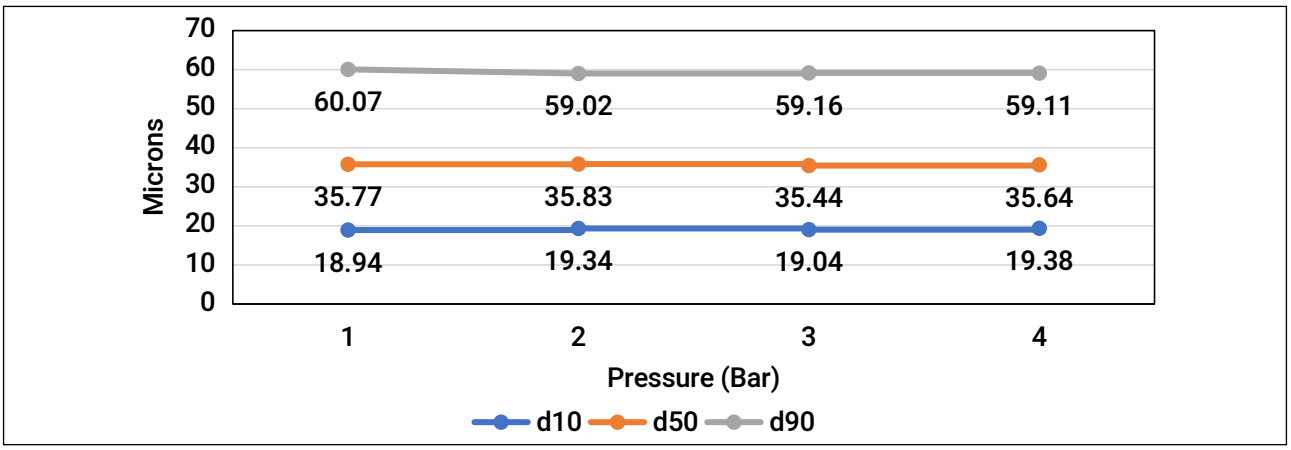


Figure 4. Values for the d10, d50 and d90 of Sodium starch glycolate from different pressures

The next sample to be tested was **Sodium starch glycolate** which is used as another pharmaceutical grade dissolution excipient for tablets and capsules. Sodium starch glycolate absorbs water rapidly, resulting in swelling which leads to rapid disintegration of tablets and granules. It is used as a disintegrant, a suspending agent and as a gelling agent. Without a disintegrant, tablets may not dissolve appropriately and may affect the amount of active ingredient absorbed, thereby decreasing its effectiveness (3).

The sample was measured at 4 pressures ranging from 1-4 Bar as shown in Figure 3. Yet again this was a free-flowing material so no pre-dispersion was deemed to be required. The results at all 4 different pressures produced a perfect comparison over plot. From this visual information, it can be construed that there were no natural agglomerates and that there was a very small population of fines less than 2 microns in size. To find more specific information, the d10, d50 and d90 values were exported to an excel spreadsheet as shown in Figure 4.

As Sodium starch glycolate is a finer product than MCC, there will be a lot more particles to measure per gram of material and hence the feed rate can be reduced without affecting the repeatability even with a smaller amount of sample being measured in the test time. We can see from the results that the d10, d50 and d90 values are totally consistent from 2-4 Bar pressure. The only slight difference is on the d90 at 1 Bar pressure where its size was 60.07 microns which was 1.5% higher than the d90 values for 2-4 Bar pressure.

So for a perfect result any measurements made on this material should be made in the 2-4 Bar pressure range. My preference would be to measure MCC at 3 Bar pressure and the d10 at this pressure is 19.04 microns, d50 is 35.44 microns and the d90 is 59.16 microns.

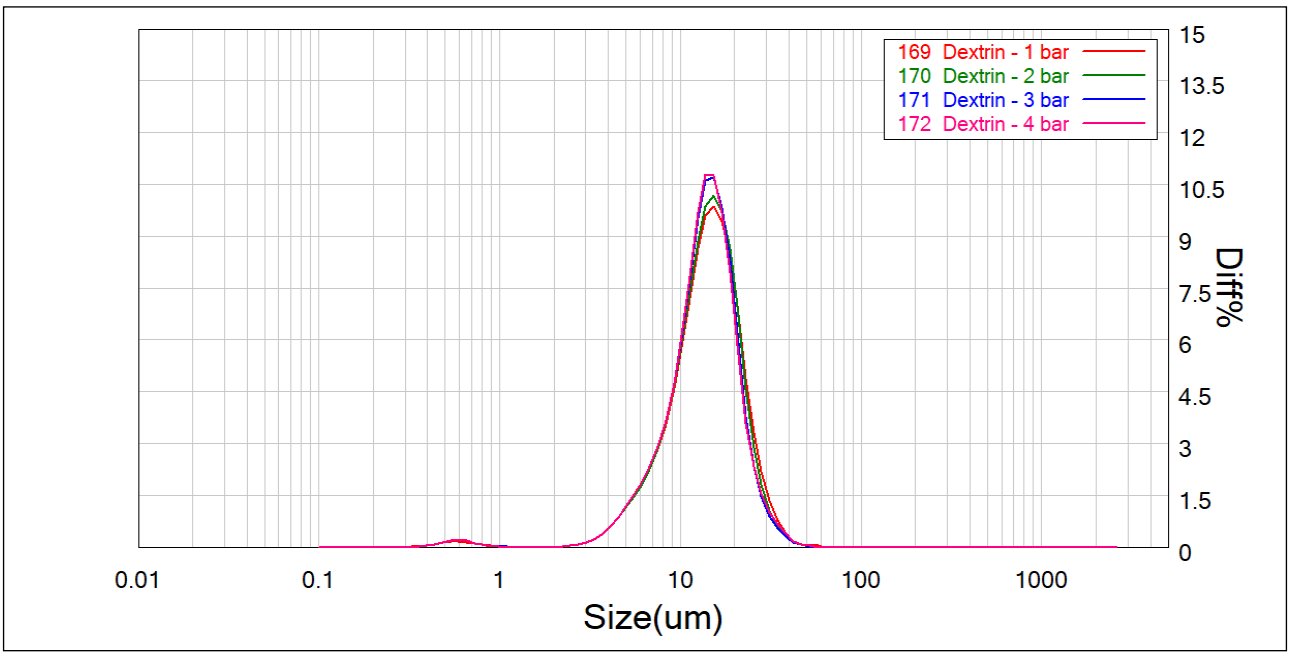


Figure 5. Dextrin particle size distribution from different pressures

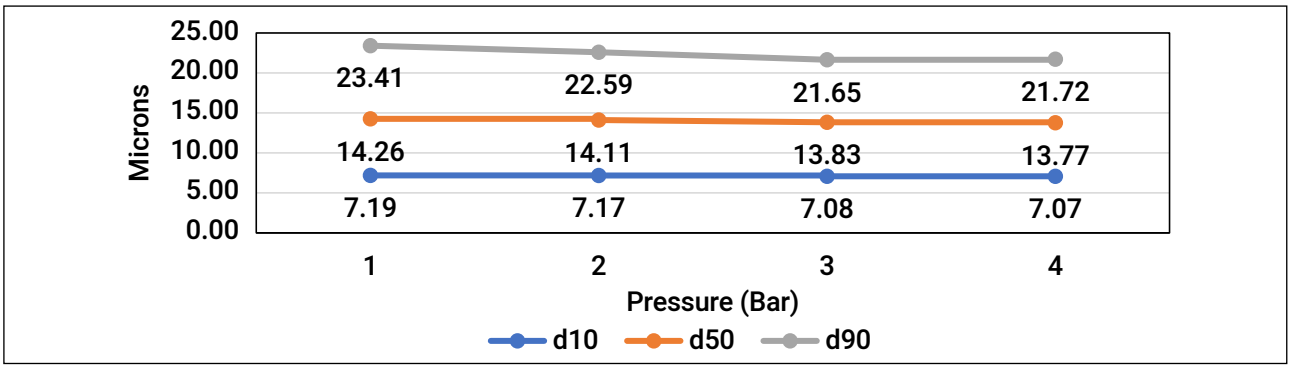


Figure 6. Values for the d10, d50 and d90 of Dextrin from different pressures

Dextrin is a thickening and binding agent for pharmaceuticals and consists of a group of low-molecular-weight carbohydrates produced by the hydrolysis of Starch or Glycogen. They are mixtures of polymers of the D-glucose units linked by alpha-(1->4) or alpha-(1->6) glycosidic bonds. It is used for investigations in the treatment of cancer/tumors and solid tumors (4).

It was measured at pressures varying between 1-4 Bar without any pre-dispersion as shown in Figure 5.

As Dextrin is finer than Sodium starch glycolate, there will also be a lot more particles to measure per gram in the same test time and hence the feed rate can be further reduced without affecting repeatability. We can see from the comparison graph that on first viewing the graphs seem to overplot very well at all pressures. However, on closer inspection we can see that between 20-50 microns, the overplot is not quite so good. At this point it is necessary to export the d10, d50 and d90 values to an excel spreadsheet to evaluate where the optimum pressure range lies. For the d90, there is a steady decrease in value from 23.41 to 21.65 microns at 3 Bar as shown in Figure 6. The result at 4 Bar is the same as at 3 Bar which implies that slight deagglomeration of the sample took place from 1-3 Bar and the result was stable from 3-4 Bar pressure. The same can be said for the d50 and d10 values. It is thus safe to conclude that the optimum working pressure range for Dextrin is between 3-4 Bar pressure. I would choose 3 Bar and the results for this Dextrin sample are 7.08 at the d10, 13.83 microns at the d50 and 21.65 microns at the d90.

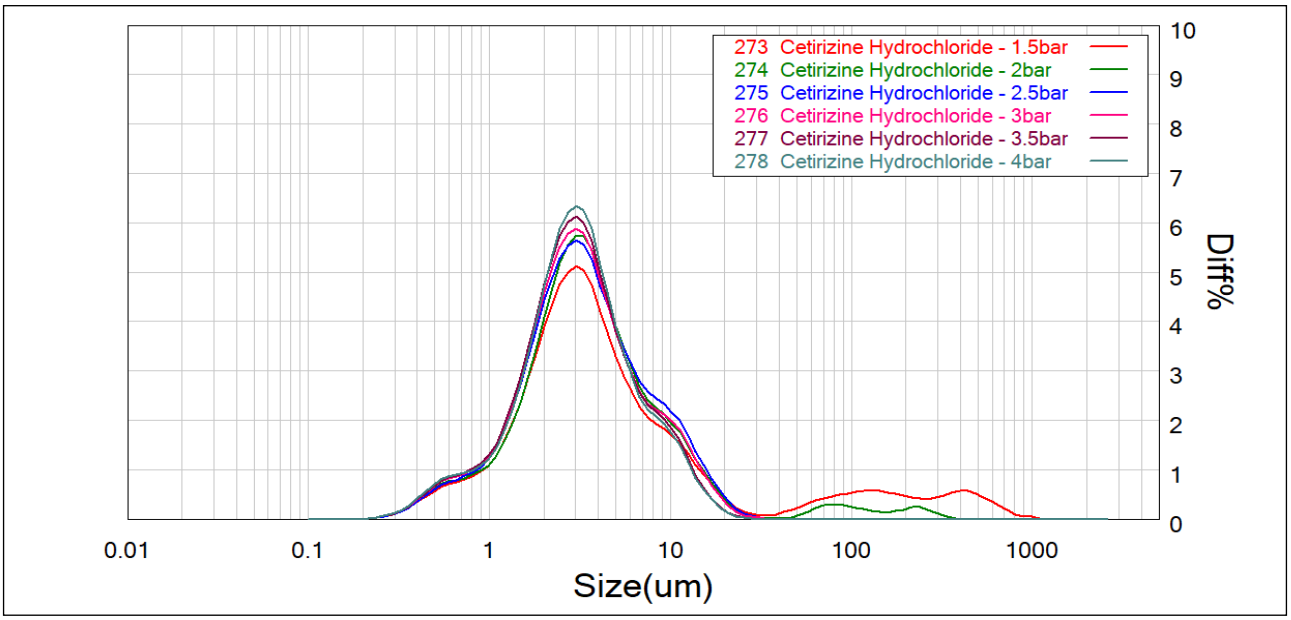
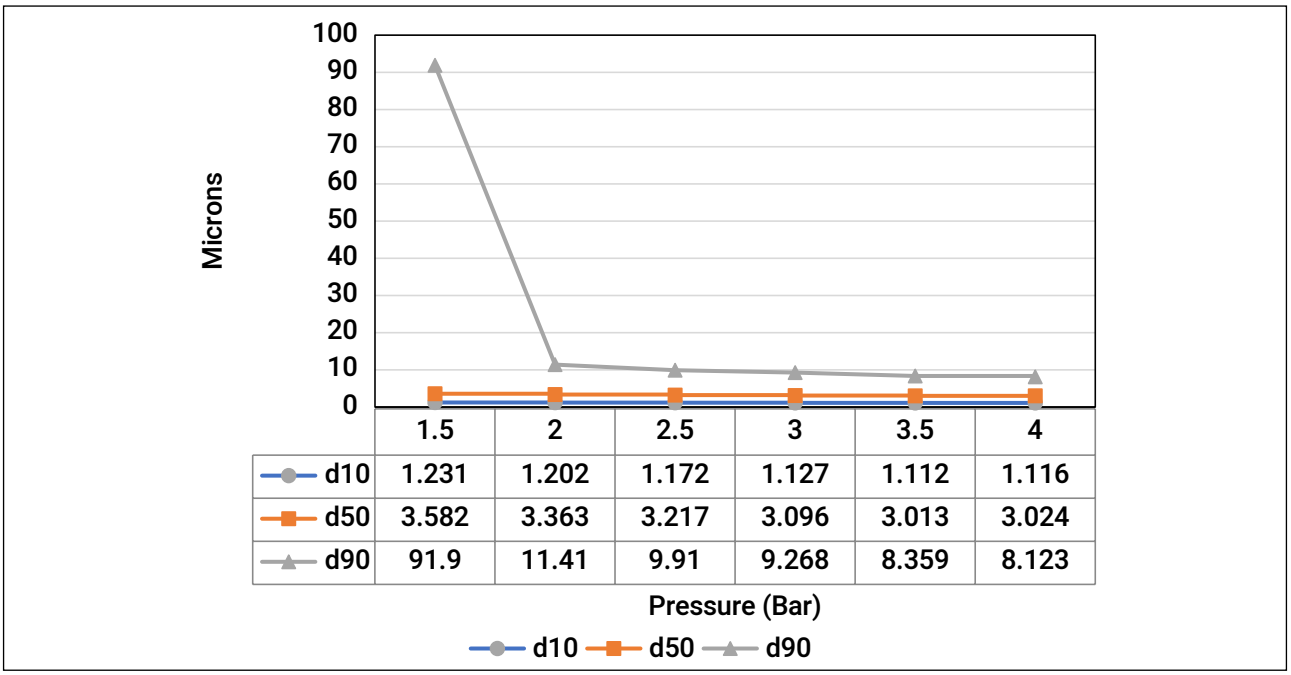


Figure 7. Cetirizine Hydrochloride particle size distribution from different pressures



	1.5	2	2.5	3	3.5	4
d10	1.231	1.202	1.172	1.127	1.112	1.116
d50	3.582	3.363	3.217	3.096	3.013	3.024
d90	91.9	11.41	9.91	9.268	8.359	8.123

Figure 8. Values for the d10, d50 and d90 of Cetirizine Hydrochloride from different pressures

Cetirizine Hydrochloride is an antihistamine used to relieve allergy symptoms such as watery eyes, runny nose, itching eyes/nose, sneezing, hives, and itching (5). It was measured at 6 different pressures ranging from 1.5 to 4 Bar as shown in Figure 7. Because it has a much finer particle size range than the previously measured samples, it is advisable that it be pre-dispersed using the sieve pan and tapped sieve method described earlier.

For these tests, this pre-dispersion method was not taken advantage of, however as can be seen from the comparison data above, the agglomerates are visible only at pressures from 1.5 to 2 Bar.

It is worthy to note that once the red and green distribution curves for the 1.5 and 2 Bar analyses are excluded, we can see that the particle size range lies between 0.2 and 30 microns. We know that at pressures higher than 2.5 Bar there were no obvious agglomerates but to see exactly at what pressure or pressure range we should be working in, we need to export the data to excel and look at the numbers as shown in Figure 8.

When looking at the exported data for d90, we can see that all agglomerates have been dispersed when a pressure of 2.5 Bar has been reached. There is a steady slight decrease in the values for d10 d50 and d90 at increasing pressures greater than 2.5 Bar. For this reason it would be most wise to measure this sample at 2.5 Bar pressure and pre-disperse the sample using the sieve and sieve pan method described earlier.

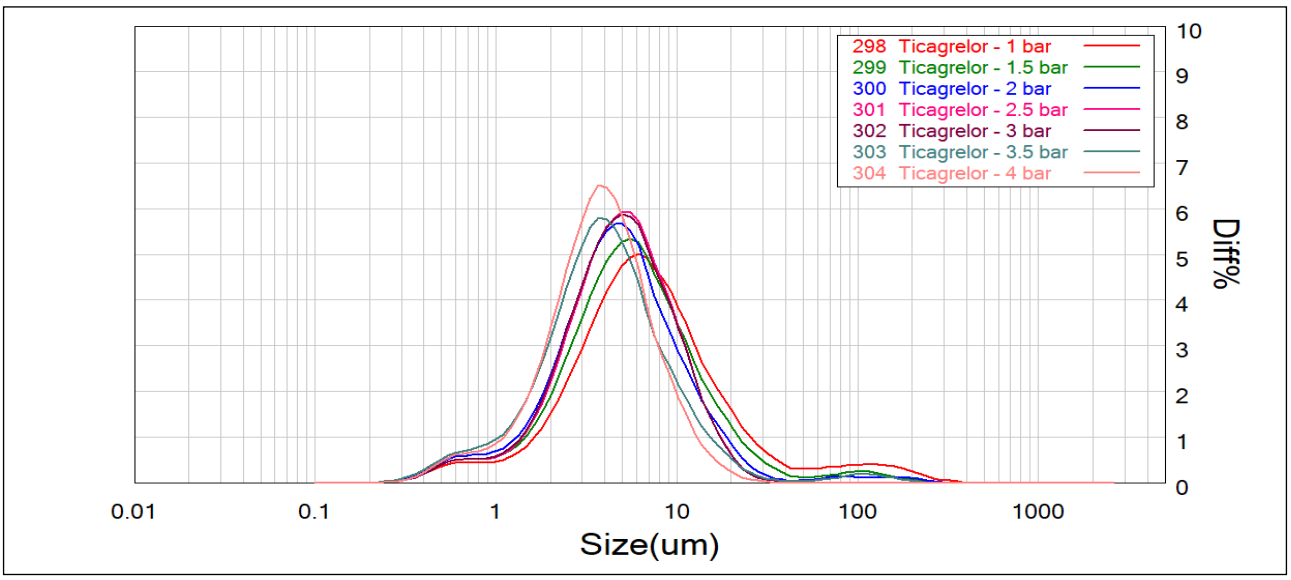
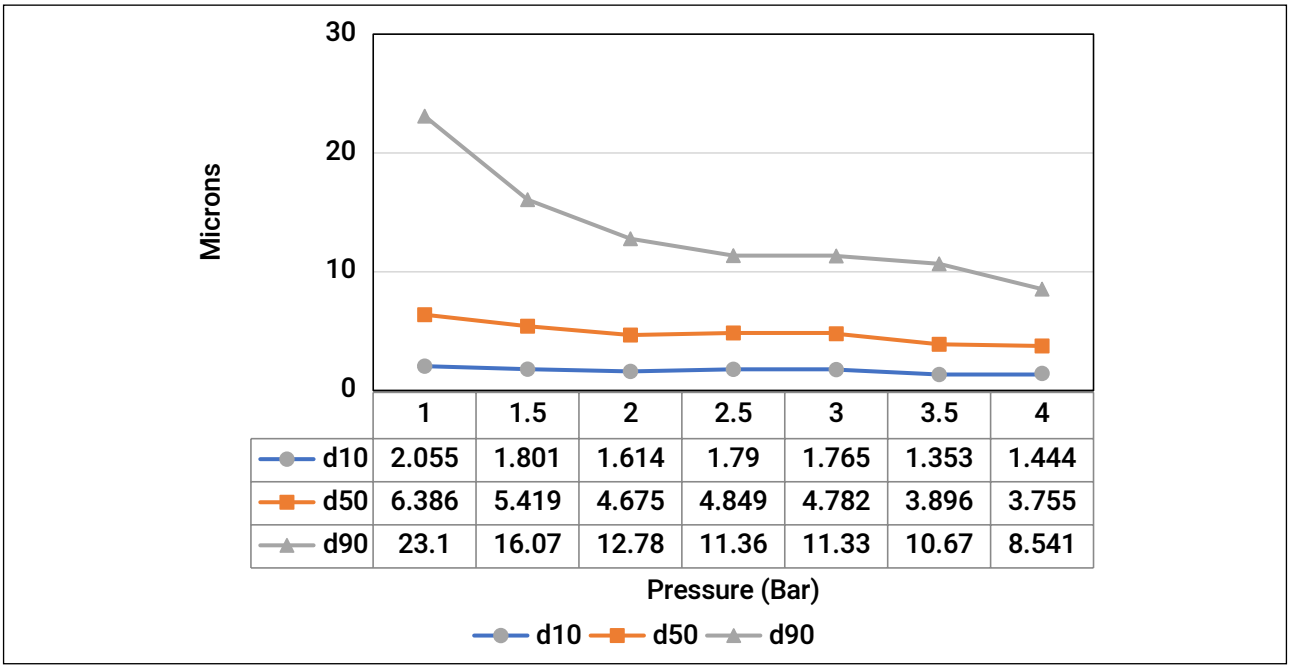


Figure 9. Ticagrelor particle size distribution from different pressures



	1	1.5	2	2.5	3	3.5	4
d10	2.055	1.801	1.614	1.79	1.765	1.353	1.444
d50	6.386	5.419	4.675	4.849	4.782	3.896	3.755
d90	23.1	16.07	12.78	11.36	11.33	10.67	8.541

Figure 10. Values for the d10, d50 and d90 of Ticagrelor from different pressures

Ticagrelor is an antiplatelet medicine. It makes the blood flow through your veins easier, meaning your blood will be less likely to form a dangerous blood clot.

Taking ticagrelor can help prevent blood clots if you are at risk of having them (6).

This sample is fine and highly static, so for this reason the sieve and sieve pan method should be used to pre-disperse the sample. If we look at the comparison graph in Figure 9, we can see that at lower dispersion pressures, there is evidence of agglomerates above 35 microns which need to be dispersed by higher pressure dispersion air. The best way of finding a working pressure range will be to look at the export data in Figure 10.

Looking at the d90 values from 1-4 Bar we can a classic S-Curve where the sample is deagglomerated from 1-2.5 Bar. Beyond 3 Bar pressure we can see some breakage of the crystalline material. At the inflection point (2.5-3 Bar) there is no change in the results, so this is our working pressure range, and I would choose 3 Bar as the optimal working pressure with results for d10 at 1.765, d50 at 4.782 and d90 11.33 microns.

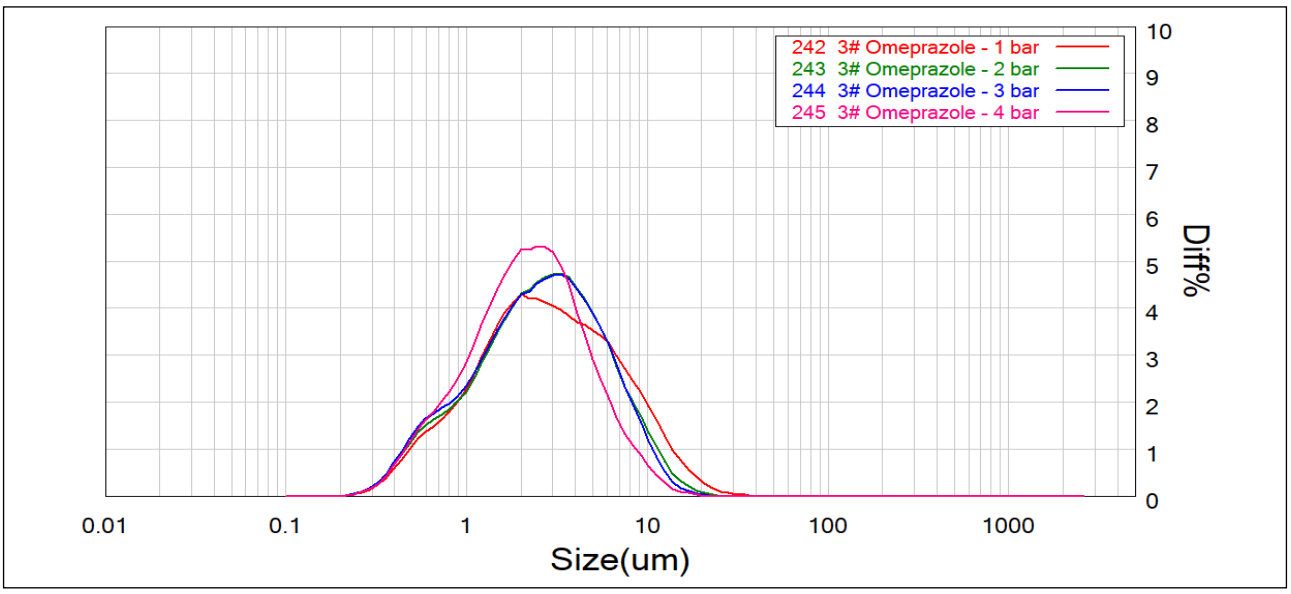


Figure 11. Omeprazole particle size distribution from different pressures

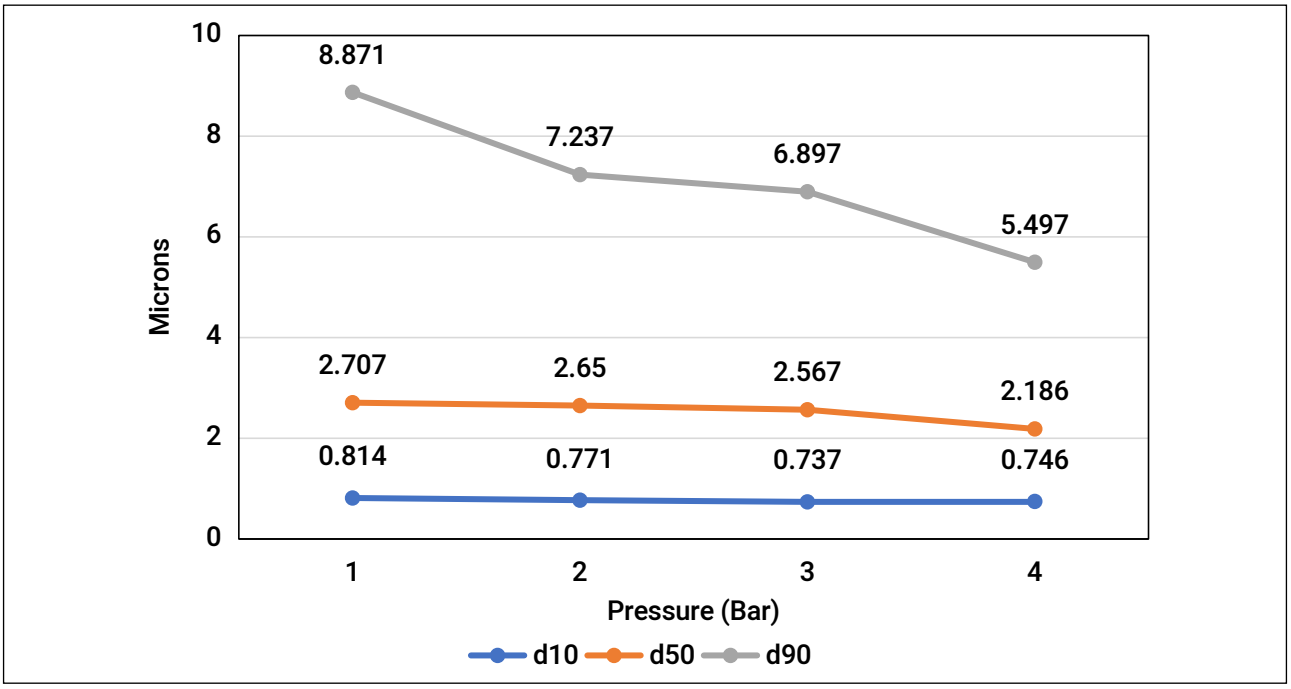


Figure 12. Values for the d10, d50 and d90 of Omeprazole from different pressures

Prescription **Omeprazole** is used to treat the symptoms of gastro-oesophageal reflux disease (GERD). This is a condition in which backward flow of acid from the stomach causes heartburn and possible injury of the oesophagus (the tube between the throat and stomach) in adults and children 1 year of age and older (7).

It was measured at 4 pressures ranging from 1-4 Bar. We can see from the comparison plot in Figure 11 that it is much more easily dispersible than other API,s of this primarily sub 20-micron size. Let us have a look at the exported data in the titration curve as shown in Figure 12.

We have deagglomeration taking place between 1-2 Bar and breakage from 3-4 Bar.

However, looking at the S-curve shaped D90, there is a definite inflection between 2 and 3 Bar where the results show minimal change. This is the pressure range within which we would be able to confidently make repeatable measures and I would recommend the 2 Bar pressure where the d10 is 0.771, the d50 is 2.65 and the d90 is 7.237 microns.

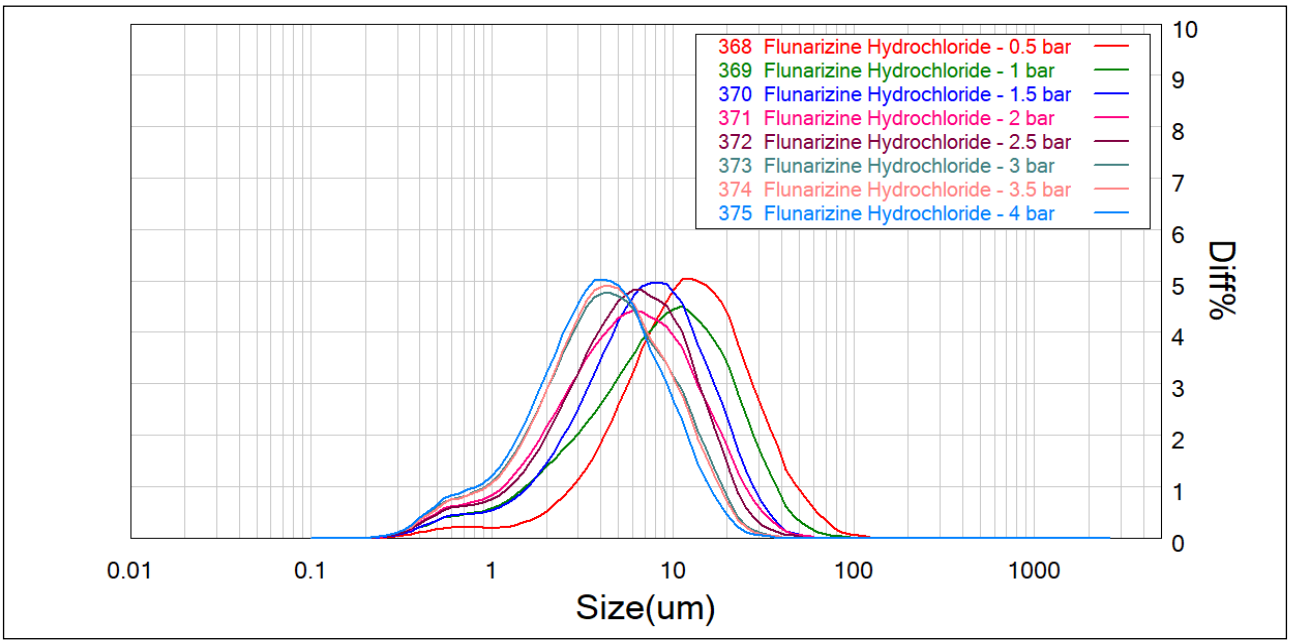


Figure 13. Flunarizine Hydrochloride particle size distribution from different pressures

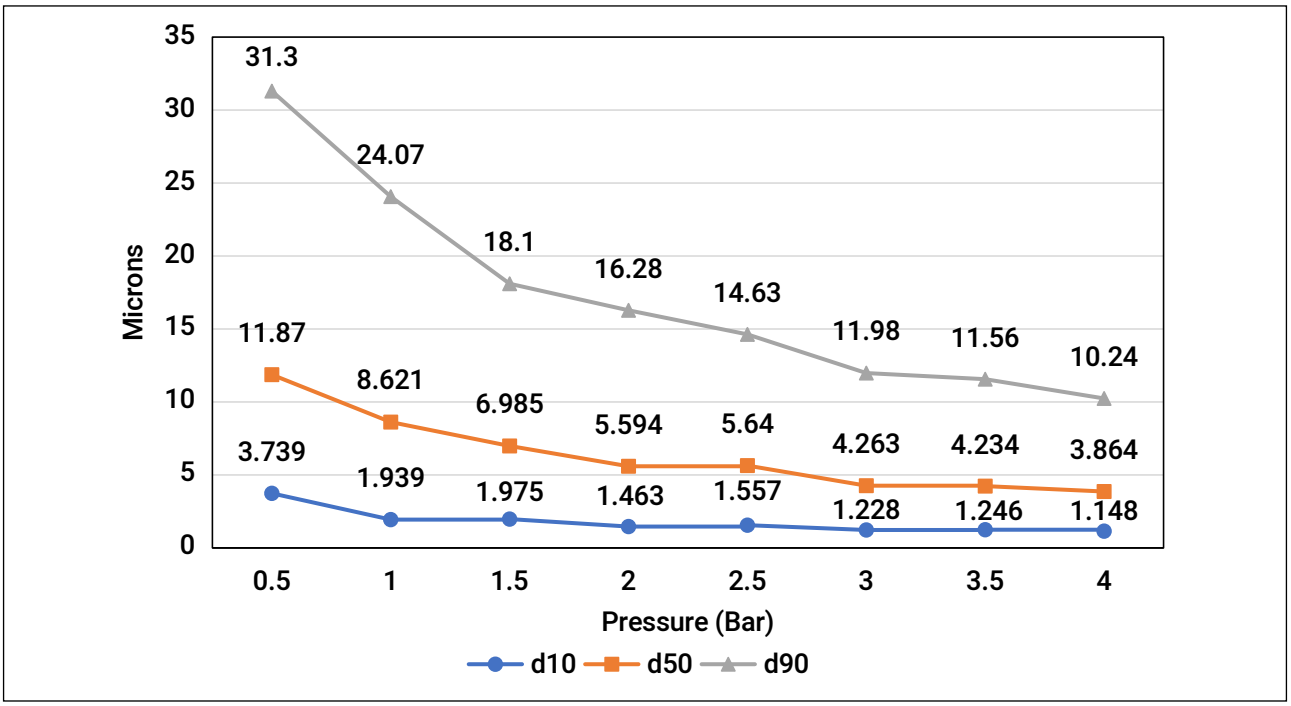


Figure 14. Values for the d10, d50 and d90 of Flunarizine Hydrochloride from different pressures

Flunarizine Hydrochloride is a selective calcium entry blocker with calmodulin binding properties and histamine H1 blocking activity. It is effective in the prophylaxis of migraine, occlusive peripheral vascular disease, vertigo of central and peripheral origin, and as an adjuvant in the therapy of epilepsy (8).

As can be seen from the comparison plot in Figure 13 the smallest size is unchanging but the maximum size shifts dramatically over the pressure range from 0.5 to 4 Bar pressure. The only way to further analyse this sample is by looking at the pressure titration curve in Figure 14.

As we can see, there are only 2 points of inflection on this titration curve if we look only at the d10 and d50 percentile points and they range between 2-2.5 Bar and 3-3.5 Bar. When investigating the d10 and d50 results for both the 2-2.5 Bar and 3-3.5 Bar ranges there is good repeatability. As we should always look for the first inflection point for similar results, a dispersion pressure at 2 Bar should be chosen.

Magnesium stearate is a fine white powder that sticks to your skin and is greasy to the touch. It's a simple salt made up of two substances, a saturated fat called stearic acid and the mineral magnesium.

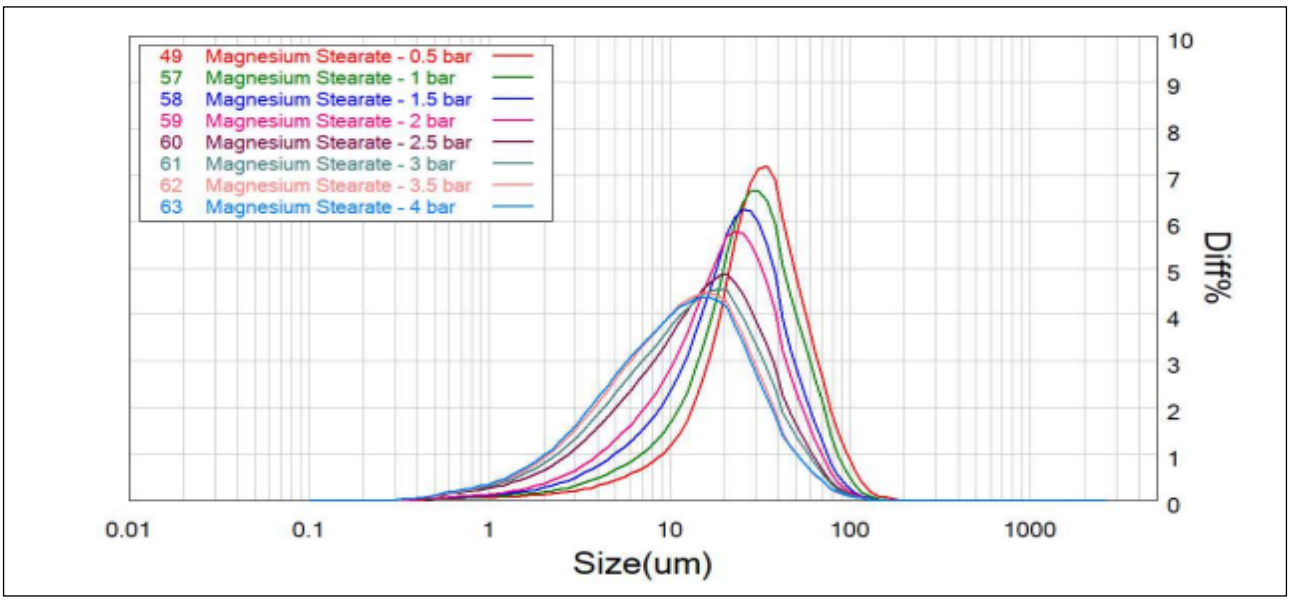


Figure 15. Magnesium stearate particle size distribution from different pressures

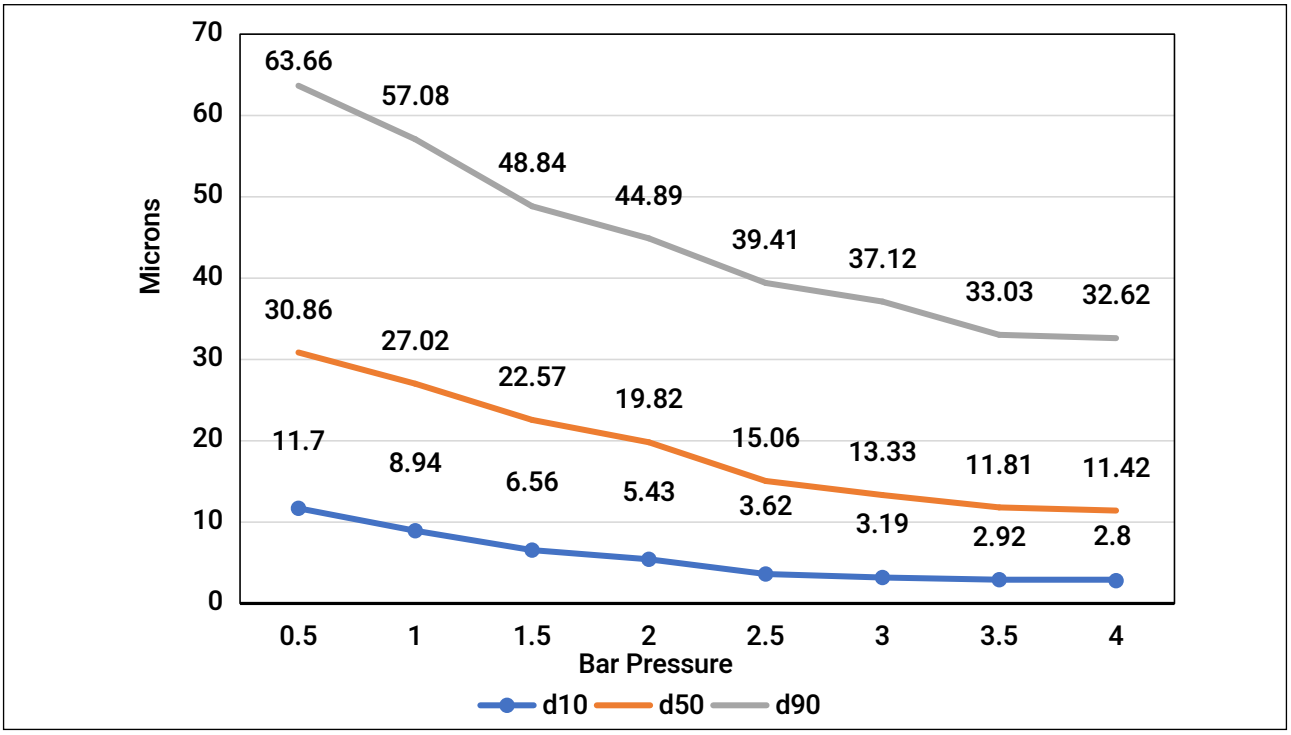


Figure 16. Values for the d10, d50 and d90 of Magnesium stearate from different pressures

Magnesium stearate is the most used metallic salt boundary lubricant containing two equivalents of a fatty acid (usually stearic and palmitic acid) and a charged magnesium. Magnesium stearate is an additive that's primarily used in medication capsules. Its primary role is to prevent the individual ingredients in a capsule from sticking to each other and the machine that creates the capsules. It helps improve the consistency and quality control of medication capsules. It's possible to create medication capsules without magnesium stearate, but it's more difficult to guarantee the consistency and quality of those capsules. Magnesium stearate is used to delay breakdown and absorption of medications, so they're absorbed in the correct area of the bowel (9).

The analysis above in Figure 16 shows that maximum sized particle is 167 microns, and the smallest particle is between 0.3-0.4 microns dependent on the pressure. If we look closely at the titration curve shown in Figure 16, we can see that the material which we know is very sticky only is fully dispersed at higher pressures. In fact, there is no point of inflection till a pressure of 3.5 Bar is reached. It is safe to say that full dispersion is not attained until we have reached a pressure of 4 Bar.

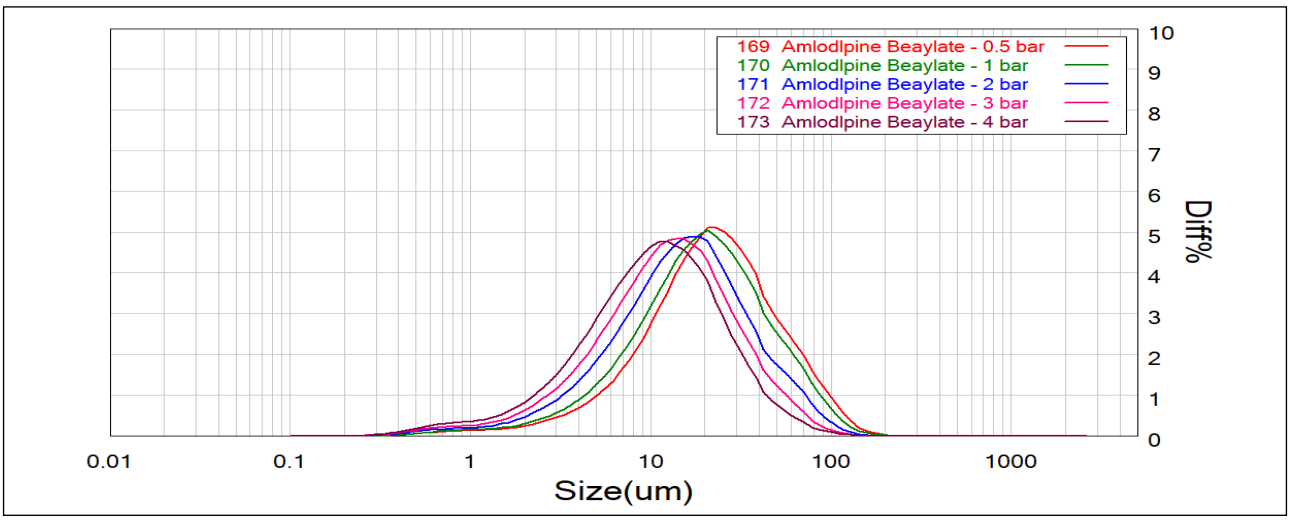


Figure 17. Amlodipine Besylate particle size distribution from different pressures

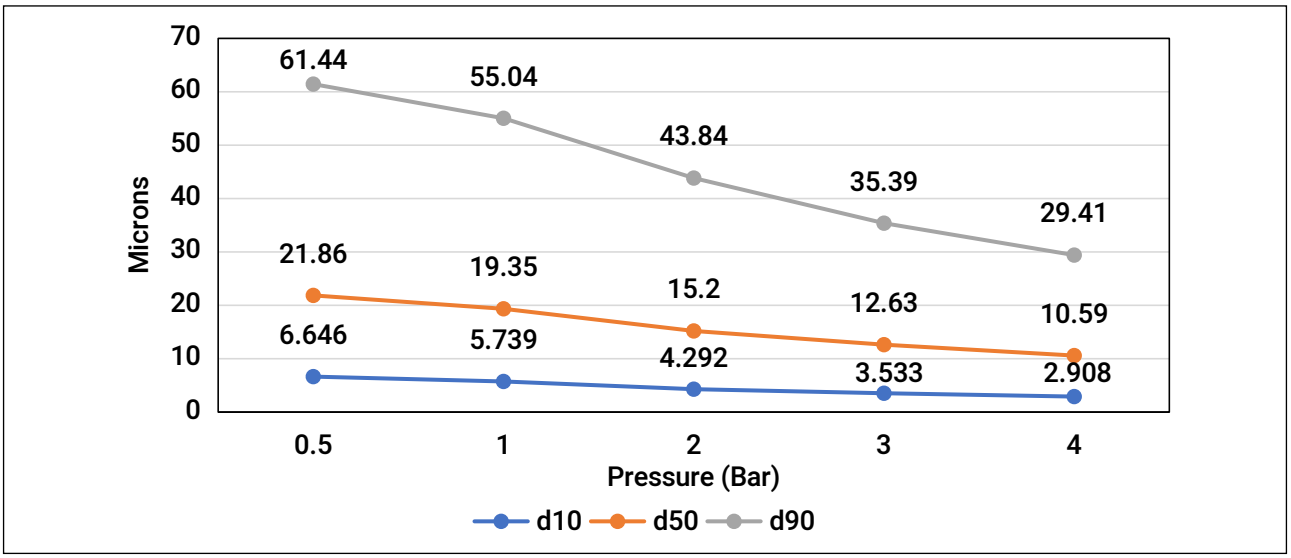


Figure 18. Values for the d10, d50 and d90 of Amlodipine Besylate from different pressures

Amlodipine Besylate is a medicine used to treat high blood pressure (hypertension). If you have high blood pressure, taking amlodipine helps prevent future heart disease, heart attacks and strokes. Amlodipine is also used to prevent chest pain caused by heart disease (angina) (10).

From the comparison plot in Figure 17, we see that the maximum size is somewhere in between 150 and 200 microns, whilst the smallest particle size is 0.3 microns for all pressures. If we look at the titration curve in Figure 18, we can see that the only pressure range where there is anything close to a point of inflection lies somewhere between 0.1 and 1 Bar. Above 1 Bar, there appears to be breakage of the crystalline material. Measurements below 0.5 Bar pressure would probably confirm a working pressure range between 0.2 and 0.5 Bar. As no measurement at 0.2 Bar has been made, we can only make a recommendation on what we know and the closest result would appear to be at 0.5 Bar where the d10 is 6.646, the d50 is 21.86 and the d90 is 61.46 microns.

Discussion

A review of the results in terms of comparison data showed in some samples that there was good enough repeatability to judge that they dispersed well at all pressure settings. However for other samples this was not clear enough and that we needed to review the data exported to excel to produce a pressure titration curve to look at the d10,d50 and d90 parameters in a different way to give greater insight as to which pressures provided better dispersion and which ones produced breakage of the particles. Analysis of these titration curves showed that the 9 different pharmaceutical samples can be split into 5 groupings.

The first group is made up of the MCC and Sodium Starch Glycolate which performed in similar ways when looking at the titration curve. The results showed that the Sodium Starch Glycolate measured more or less the same particle size distribution at all pressures. However the MCC behaved slightly differently in that repeatable results were achieved between 1 and 2 Bar so full dispersion of the sample had already been achieved up to 2 Bar. On the other hand, although the d90 at 3 and 4 bar remained the same, an 8% reduction in size of the d50 and a 20% reduction of the d10 in size was probably due to milling. Thus it safe to say that the MCC pressure measurement range should be 1-2 Bar.

The second group only contained only Dextrin as the comparison results also looked very good but by only looking at the titration curve can we find the perfect pressure range. On the surface it followed a different classic titration curve where the sample appears very well dispersed but only by looking for absolute repeatability of the d10, D50 and d90 can we see that full dispersion takes place at 3 bar and the results at 4 Bar yield the same result. Thus we can be fully confident in making the pressure setting in the range between 3 and 4 bar to achieve accurate results we can trust.

Group 3 contains Omeprazole and Cetirizine Hydrochloride because they both have the same initial dispersion phase. In the case of Cetirizine Hydrochloride, we can see from the comparison graph that there is evidence of obvious agglomeration at 1.5 and 2 Bar but none at 2.5 bar. When we look at the pressure titration we can see there is a gradual small decrease in size for the d10, d50 and d90 values from 2.5 to 4 Bar. From this we can deduce that 2.5 Bar is the most appropriate pressure to use. Omeprazole is slightly different in that full dispersion appears to have taken place at 2 bar pressure and milling breakage of particles beyond that point.

Group 4 contains Ticagrelor and Flunarizine Hydrochloride and when you look at the comparison graph, it seems confusing. So only by looking at the pressure titration can we solve this search for the optimal pressure or pressure range. This is a classic S shaped titration curve for the Ticagrelor sample with deagglomeration taking place from 1 to 2.5 bar. At 2.5 Bar there is an inflection in the curve up to 3 Bar, so repeatable results were achieved between 2 and 3 bar. Above this pressure, milling occured for all 3 parameters so 2-3 Bar is the working pressure range. In the case of Flunarizine Hydrochloride, deagglomeration is taking place from 0-2 Bar, stable repeatable results are measured between 2 to 2.5 Bar for the d10 and d50 but a slight decrease in size of the d90. Milling of particles occurs above 2.5 bar. As the d10 and d50 are similar at 2 and 2.5 bar but milling of the d90 particles appears to be occurring above 2 Bar, my choice of dispersion pressure would be 2 Bar for this sample.

Group 5 contains Magnesium stearate and Amlodipine Besylate and in both cases there is a gradual reduction in the d10, d50, and d90 from 0.5 to 4 bar. There are no clues in the comparison graphs and no inflections in the titration curves. For these samples we have to look for further information to assist us in finding the correct pressure. The first thing we can do is look at results from pressures ranging from 0.1 to 0.5 Bar to ascertain if sample has been dispersed already before 0.5 bar. The other possibility is look at digital image analysis to look at the particles and how they change at different pressures. The final possibility is to find an accurate successful wet analysis and compare it to the closest dry analysis pressure.

Conclusions

Most of the time consuming wet analysis tests performed within the pharmaceutical industry today could be easily be replaced by dry measurements using the guidelines I have explained already. Initial thorough dry testing at all pressures using the pressure titration curves will in most cases yield an appropriate working pressure or pressure range. Dry powder Laser diffraction particle size analysis provides the speed repeatability and ease of use required by the pharmaceutical in dustry. There are some samples where further future work should take place on an on-going basis and these should involve digital image analysis, lower pressure ranges and comparison with wet analysis results.

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