Amethyst

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Team Alchemist

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Homogenization technique that doesn't work on stop-check-go approach.

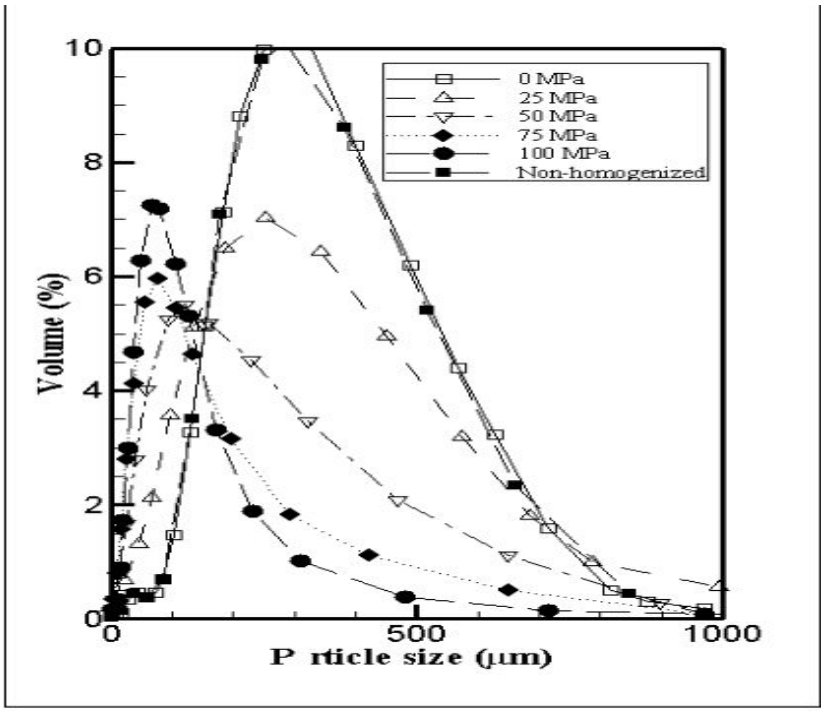
To design a process that doesn't work on stop-check-go approach, it is important to be able to estimate the time that it would take to achieve particle size as a function of the operating pressure, temperature and flow rate.

The question asks us to investigate the development of particle size with time (or with number of cycles). During the initial few cycles, the **droplet size is going to decrease** with every successive cycle due to repeated process of homogenization, but due to the **asymptotic effect of number of passes**(i.e., the subsequent processes have a smaller impact on PSD when compared with the previous process using the same homogenization pressure), **the particle size will eventually saturate and start increasing after some time**. This is due to newly disrupted droplets are thermodynamically unstable due to the Brownian motions and high intensity turbulence on the equipment and increasing the probability of collision and coalescence of freshly formed droplets to form bigger droplets.

But since the question asks us to assume that there is no coalescence in the case of the liposomal drug, we can safely assume that overprocessing of the particle doesn't take place.

Dependence on Homogenizing pressure

The final particle size diameter varies as $\mathbf{d \propto P^{-m}}$ (where m is a positive real number and P is the homogenizing pressure). So the final **diameter of the droplet decreases as the homogenizing pressure increases.**



Dependence on Temperature

As the source temperature of the emulsion increases, the interfacial tension between the dispersed and continuous phase decreases, as a result of which the deformation of oil droplets becomes easier, and they are easily broken down into finer droplets at the exit of the valve.

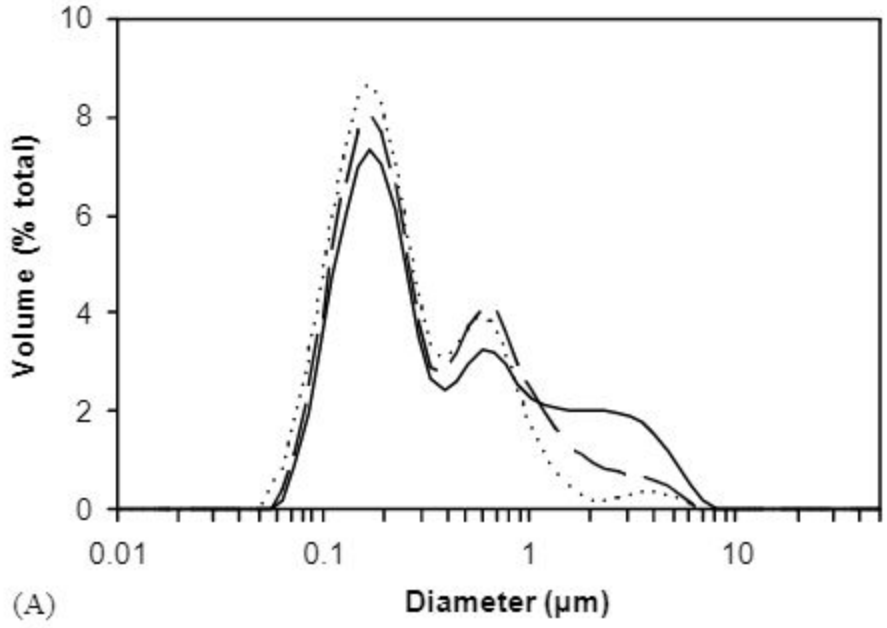


Figure: Influence of milk inlet temperature (T_{in}) at a homogenizing pressure of 200 MPa : 4°C (—), 14°C (--), 24°C (· · ·)

Dependence on Flow Rate

As the flow rate increases, the overall kinetic energy of the emulsion increases as a result of which there is greater turbulence at the exit of the valve and more emulsification.

- **So can we estimate the time it would take to achieve the desired diameter??????**

Since we do not have a direct theoretical formula to calculate the average diameter as a function of operating pressure, temperature and flow rate, we have to get an empirical formula. We have to first conduct a set of experiments and from the data collected, find empirical relations between the average diameter (or time required) and operating pressure, temperature and flow rate separately (keeping all other variables like valve and impingement design constant).

The empirical relation can look something like this

$$\text{Time} = K_1(\text{pressure})^a(\text{temperature})^b(\text{flow rate})^c$$

Where K_1, a, b, c are empirical constants which have to be found out from the data obtained the experiments

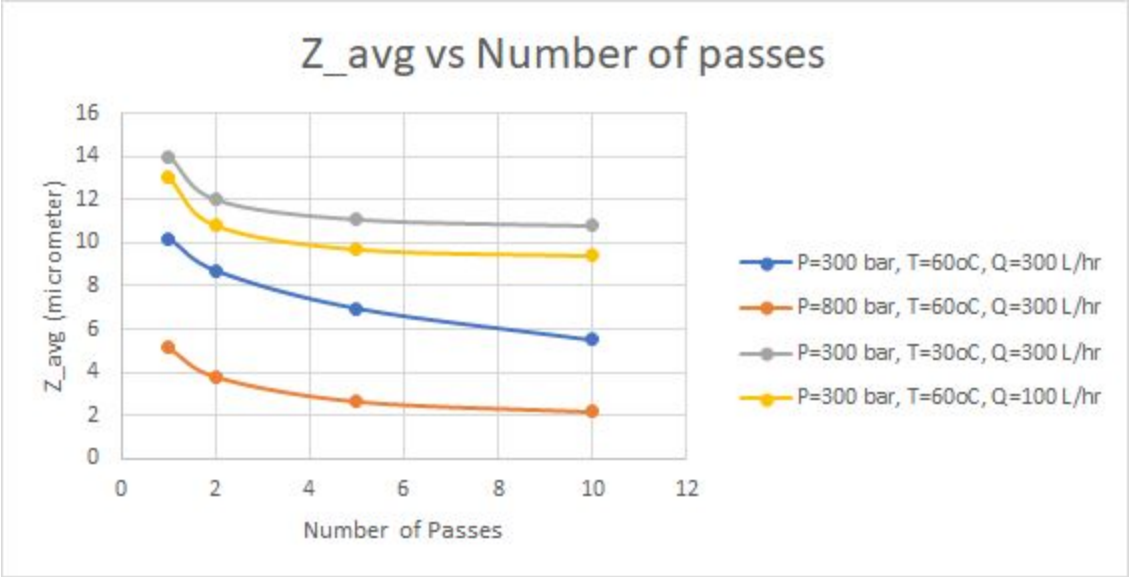
Even if we do not develop empirical relations between the independent (i.e., pressure, temperature and flow rate) and the dependent variables (i.e., time), we can prepare data tables or graphs by conducting repeated experiments, which can be immediately looked up by the operator to estimate the time it would take to achieve his desired particle size by comparing his operating conditions (pressure, temperature and flow rate) with those already given in the graph or chart.

Homogenizer Pressure(Mpa)	Temperature(oC)	Flow Rate(l/h)	Average Diameter(um)
125	45	120	1.23
125	60	140	1.16
125	75	160	1.08
145	45	120	1.17
145	60	140	1.09
145	75	160	0.98
165	45	120	0.82
165	60	140	0.75
165	75	160	0.7

Figure: This is what a data table is supposed to look like, which the operator can use for his reference to decide upon the size (assuming the time taken for all the above processes is same and equal to, say 1 hour)**.**

Plot of average particle diameter with time at different conditions

With one pass through the homogenizer, there is a certain probability that not all particles are subjected to the same intense energy of homogenization; therefore, a portion of the particles passes through without being as reduced in size as others. Another pass through the homogenizing valve increases the probability of these large particles being reduced. Therefore, **multi passing through the valve narrows the particle-size distribution**. The **number of passes also presented an asymptotic effect**, i.e., the subsequent processes have a smaller impact on PSD when compared with the previous process using the same homogenization pressure.



Number of passes	P=300 bar, T=60°C, Q=300 L/hr (Z_avg)	P=800 bar, T=60°C, Q=300 L/hr	P=300 bar, T=30°C, Q=300 L/hr	P=300 bar, T=60°C, Q=100 L/hr
1	10.2	5.16	14	13
2	8.7	3.82	12	10.8
5	6.96	2.68	11.1	9.7
10	5.51	2.2	10.8	9.4

Figure: The above values in the data table are hypothetical and provide only a qualitative idea, not a quantitative idea.

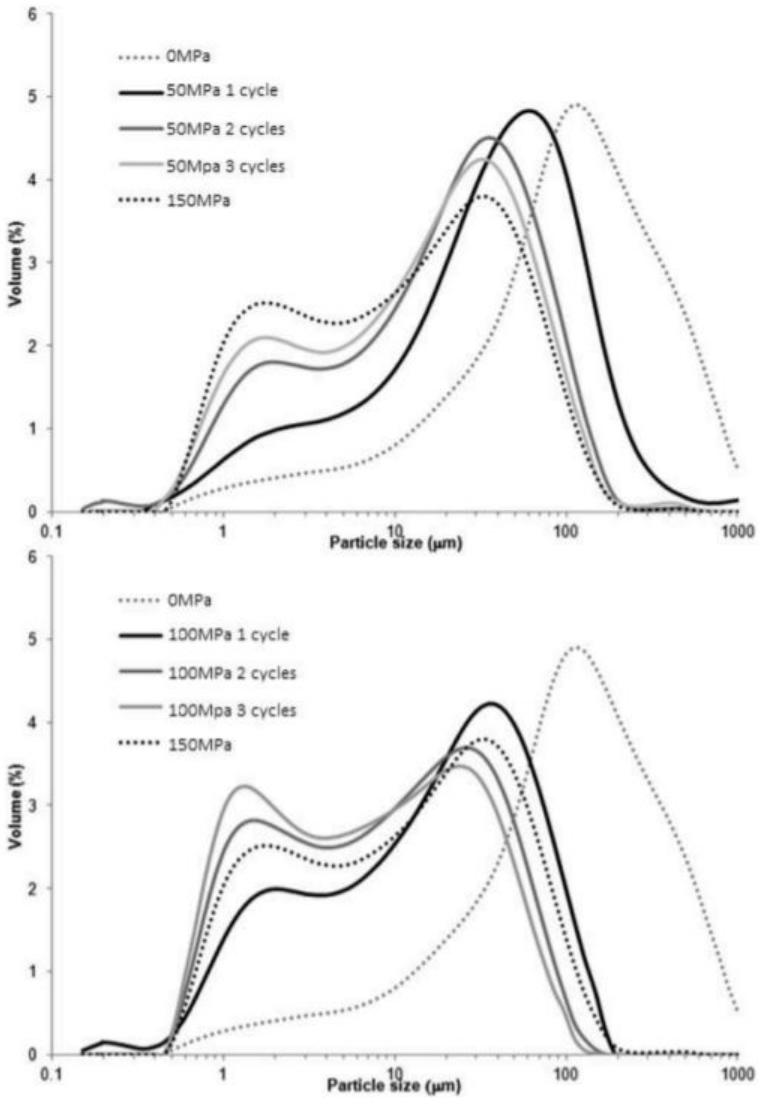


Figure: In the first figure, we can see that the size distribution follows a log-normal distribution curve. This means that the curve is asymmetrical and contains a “tail” representing oversized particles. With an increase in the number of cycles, the probability of larger particles decreases and also the distribution narrows

New strategy to match pdI utilizing both the homogenizing stages

The question states that by using a single homogenizing stage, we are able to achieve our desired d10, d50, d90 and Z_average. However, we are not being able to achieve the desired PDI by using a single homogenizing valve, and that makes us want to use a second homogenization stage.
But if we use the second homogenizing stage directly, we might be able to achieve our desired PDI, but it may lead to **changes in either or all of the other parameters**, i.e, d10, d50, d90 and Z_average, as the second homogenizing stage will lead to further emulsification, resulting in smaller sized particles than what we originally wanted.
So, the trick will be to obtain the desired d10, d50, d90 and Z_average values not **just by the sole action of the first homogenizing valve, but by the combined action of the two homogenizing stages**, which will also give us our desired PDI, which we were not able to obtain by the use of a single homogenizing stage. The idea is that a second homogenizing step helps us to get a narrower distribution of particle size (and hence a lower PDI), but since it helps in the process of emulsification by further reducing the particle size, we have to provide that compensation for the second homogenising stage by **reducing the pressure in the first stage** so the **cumulative effect of the two homogenizing stage results in our desired particle size**.

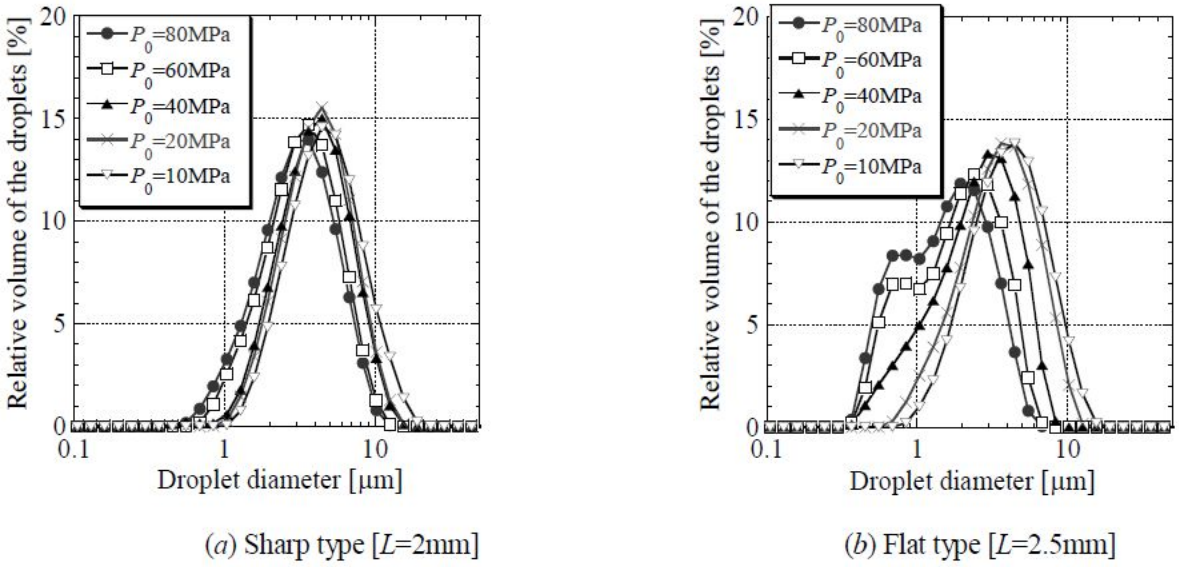
Steps to obtain the desired PDI

1. First decide upon the pressure of the second homogenizing stage, and then the first homogenizing stage to give the total pressure.
2. If a pressure gauge were positioned between the two valves, then the first and second stage could be adjusted independently, so that we get the desired particle size and PDI.

Dependency of breakage phenomena and breakage forces with different types of valves.

In any valve, the main droplet break-up occurs at the gap parallel part and the outlet jet part. . The total emulsification is the sum of effect due to the **shear stress in the parallel part of the gap** and the effect due to the **inertia force of the jet at the exit of the gap (turbulence).** In the **flat shape**, it is considered that **strong shear stress affects the emulsification at the entrance of the gap parallel part**, which it is not in the case of sharp valve, and the droplets are elongated sufficiently and are better disrupted at the exit of the gap. Hence the

emulsification is found to be better in case of flat valve than sharp valve (as can be seen from the figures below, wherein a greater fraction of particles have a diameter smaller than 1um than in the case of sharp valve).



(*a*) Sharp type [*L*=2mm] (*b*) Flat type [*L*=2.5mm]

Fig.9 Droplet size distribution (Liquid A)

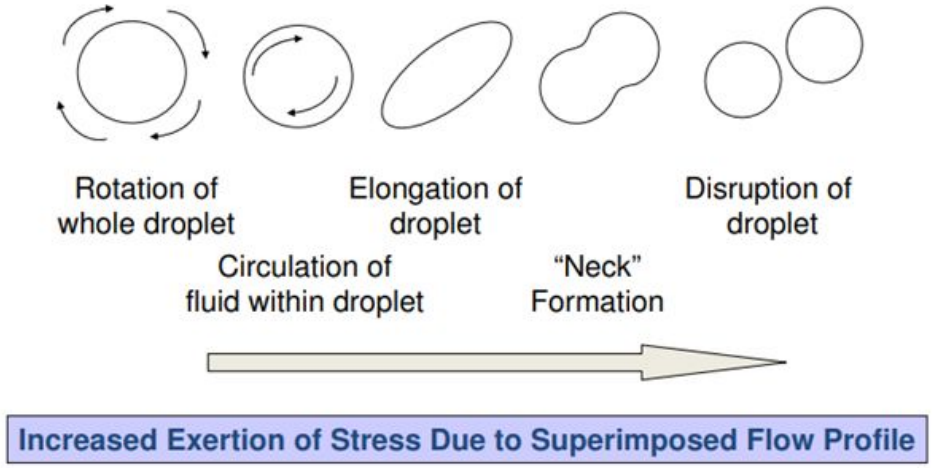
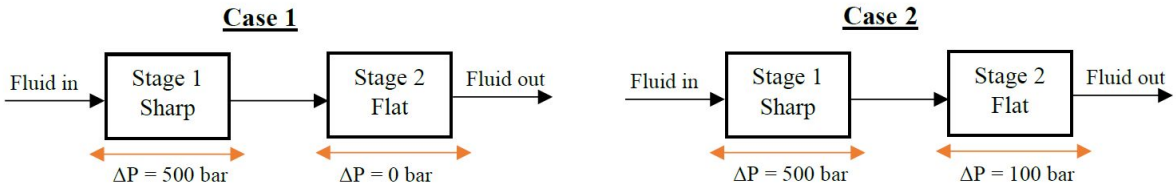


Figure: This elongation of the droplet is much better in the case of flat valve, thus leading to better disruption at the exit of the gap

Evaluation of particle size with different pressure drops in HPH with two stages of milling.



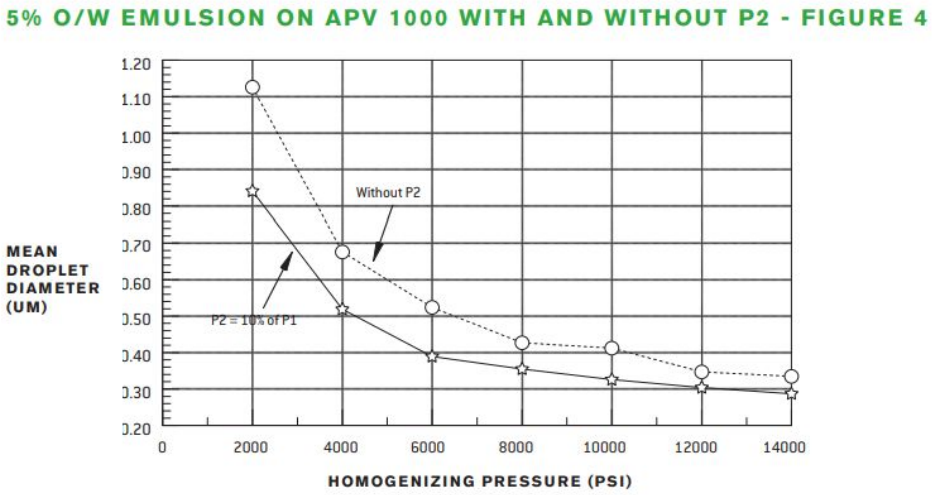
In the first case, when the pressure in the second homogenizing stage is zero, there is substantial cavitation, which creates a two-phase flow of gas-in-liquid which makes the liquid “spongy”, and the turbulence at the exit of the valve is not strong enough to break the particles into .

In the second phase, the second stage valve will exert backpressure on the fluid moving through the first-stage valve and consequently will enhance the zone of turbulence by suppressing the cavitation of the liquid.

Therefore we would see a smaller mean diameter and a narrower size distribution in the second case as compared to the first case.

However, we have to be careful that we do not operate the second stage valve at a pressure of excess than 20% of the total pressure as the mean diameter starts increasing after this point.

Note: The ratio of back-pressure and homogenizing pressure is known as Thoma Number. It is reported that cavitation decreases with increasing Th and disappears at Thoma numbers of 0.3 < Th < 0.5.



Calculation of number of cycles

Given:	Volume	=	200 L.
	Volumetric flow rate	=	300 L/hr.
	Time required to achieve the particle size	=	8 hrs

$$Time\ (min) = \frac{Volume\ (L)}{Capacity\ (L/min)} * m$$

Number of passes is calculated from the graph given below,

Since the required particle size is achieved,
f is assumed to be 0.99.

where, f is the fraction of total volume which has received P passes

From the graph, number of passes P = 4.5
So, the number of passes required is 5.

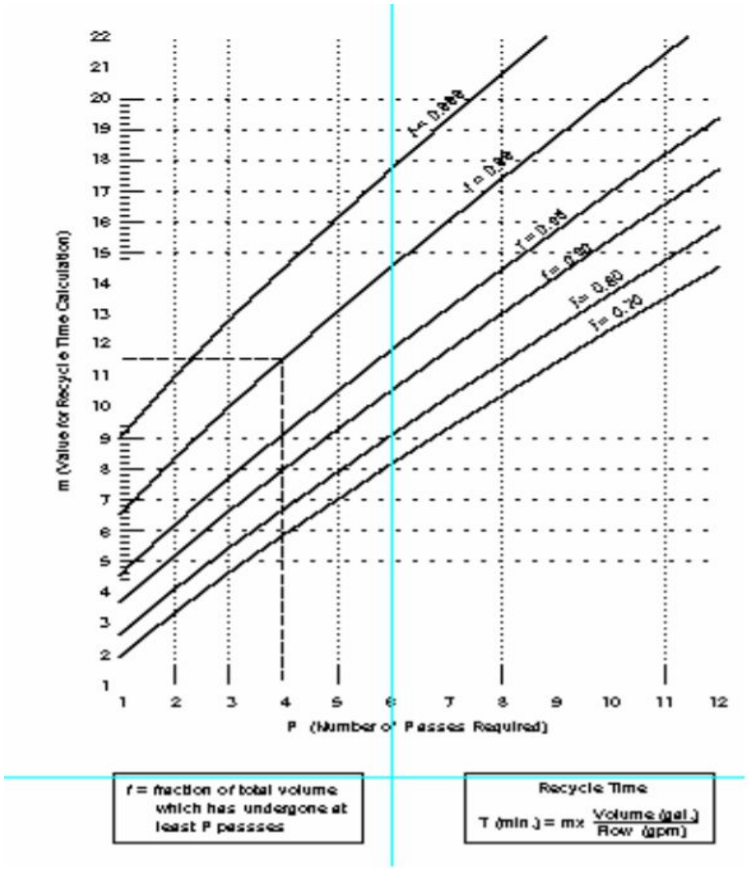


Figure: Graph from which number of passes has been obtained