Thoughts on effective pharmaceutical process plant cleaning: a practical home 'experiment' during COVID-19 lockdown

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During the UK COVID-19 lockdown, pressure washing proved much less effective than expected when applied in a domestic context. This has prompted consideration of the underlying scientific principles concerning the removal of deposits from vessel walls during product turnarounds. This analysis suggests that perhaps our confidence in validated cleaning procedures should be somewhat more conditional, and that better understanding of the cleaning process could lead to more reliable procedures and less time repeating them following quality failures.

Introduction

Sir Isaac Newton famously did some of his greatest work during his *Annus Mirabilis* straddling the years 1665 - 67 whilst in voluntary 'lockdown' in Lincolnshire, taking refuge from the Great Plague.[1] The author recently had a useful if less revolutionary moment of inspiration in the midst of a domestic chore precipitated by the extra time at home afforded by COVID-19 restrictions. Dissatisfaction with the standard of metal surface preparation achieved whilst preparing a garage door for a fresh coat of paint led to a rather crude, but nonetheless insightful, experiment and some reflections on the nature and relative magnitude of the forces which influence the success or otherwise of process equipment cleaning procedures in a variety of commonly applied techniques.

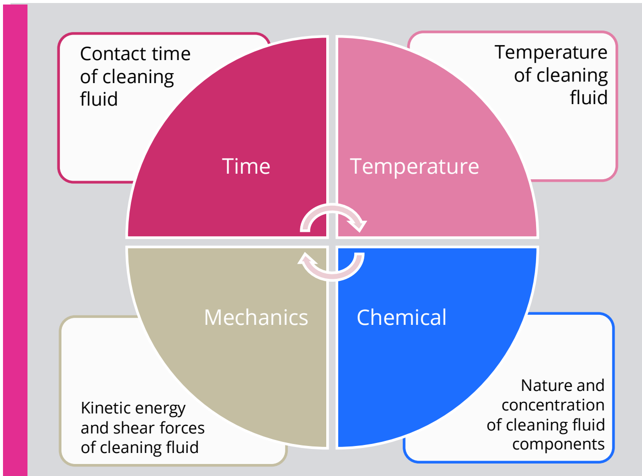

Figure 1 Sinner's Cleaning Circle

How much do we know about the mechanisms in cleaning that remove deposits from a surface? This is a topic for which the scientific literature appears to be sparse. There is some active research in the field, for example at the Universities of Limerick[2] and Birmingham[3], and at the Institute of Chemical and Engineering Sciences in Singapore[4]. In broad terms for the pharmaceutical and fine chemicals sectors however, we do not appear to be

[1] https://www.nationaltrust.org.uk/woolsthorpe-manor/features/year-of-wonders Accessed June 2020.
[2] Zhang, C, et al., *Rethinking Cleaning Validation for API Manufacturing*, Pharmaceutical Technology, September 2018, pp 42-54. Accessed August 2020.
[3] https://www.formulation.org.uk/images/stories/FormulaX/Presentations/Formula%20X%20-%20C-22%20-%20Perrakis%20Bistis.pdf Accessed June 2020.
[4] https://www.a-star.edu.sg/pips Accessed June 2020.

very much further on in our approach from 1959 when Herbert Sinner at Henkel proposed his cleaning circle (**Figure 1**) for the four driving forces for cleaning: chemical, mechanical, temperature and time.[5]

Practical Observation

Let us consider the garage door in question. The paint was old and dirty. Trying to remove some of the flaking paint with a rotating wire brush mostly added some additional rusty stains to the surface. **Figure 2a** shows the results of the decision made at this point to apply pressure washing in a bid to improve the situation. It was quite clearly a 'failure by visual inspection'! Pressure washing relies principally on the mechanical element in the Sinner's Circle. Simply wiping a finger across the surface easily removed much more grime. The door was therefore washed down manually with a sponge using a bucket of hand-hot detergent and water, achieving the results shown in **Figure 2b**. The outcome was fit for purpose, *i.e.* the door could now be repainted.

Figure 2 The garage door a) after pressure washing, b) after manual cleaning with sponge and warm detergent and water

The cleaning driving forces for manual cleaning are assessed in **Table 1**. Given that this was a domestic task, best scientific practice was not followed, and several variables were changed at once, however the earlier finger wipe makes it clear that only the change to the mechanical drivers is of any great significance.

Table 1 Driving forces for manual cleaning

	Time	**Temperature**	**Chemical**	**Mechanics**
Pressure washing garage door	Very short contact time	Cold (water mains)	Tap water	High velocity, directed, approx. perpendicular to surface
Manually cleaning garage door	Short contact time	Warm (hand hot)	Detergent in tap water	Low velocity, directed parallel to surface

[5] Sinner, H, *Über das Waschen mit Haushaltwaschmaschinen: in welchem Umfange erleichtern Haushaltwaschmaschinen und -geräte das Wäschehaben im Haushalt?*, Volume 8 of Haus und Heim, Ed. 2. Haus+Heim-Verlag, (1960)

Discussion

What can be learned from the garage door?

Let us now try to relate these observations to the practicalities of cleaning a process vessel, starting with some further observations on the initial (failed) pressure washing. The first thing to notice is that as water streams out of the area of initial impact of the spray with the surface it becomes a thin film running down the door. The thickness of this film will be controlled by gravity and the physical properties of the wash water. It can be shown that the flow regime in such circumstances is laminar. It may be inferred that the grime on the door is not very soluble in water and is firmly attached to the surface, and that much of it is probably either algal or microbial in nature.

Several concerns are raised by this example when considering cleaning and turnaround of pharmaceutical process plant.

1. Pressure jetting is usually considered to be an extreme form of the mechanical cleaning driving force. Its failure in a simple domestic setting calls into question the confidence placed in its efficacy for process vessels. This would also apply to cleaning nozzles and spray heads typically used in Clean-in-Place (CIP) systems.
2. Lack of understanding of the nature of and assumed solubility of the deposits being removed risks overconfidence in the effectiveness of the cleaning methods employed. In the 'experiment', analysis of the washings from the door would in principle have indicated that the surface was 'clean' when clearly it was not.
3. How confident is it possible to be that with the normally difficult lighting conditions within a typical process vessel, that a visual inspection will reliably detect thin and widespread deposits especially on stainless steel or blue-glassed surfaces?

Areas of concern for plant cleaning

- *Is confidence in the efficacy of pressure jetting misplaced?*
- *Does a lack of understanding or assumptions about deposits and their solubility risk overconfidence in the effectiveness of cleaning methods?*
- *How much confidence can be placed in visual detections made under difficult lighting and access conditions?*

On the other hand, the observation that finger rubbing substantially removed the grimy deposits suggests that a reasonably high degree of confidence in swab tests is justified, with the obvious caveat that by its very nature a swab test is extremely localised in the area sampled.

What is to be learned then from the effectiveness of manual cleaning of the garage door? Most certainly it is *not* that we should routinely carry out confined space entries for manual cleaning! The message is that mechanical driving forces for cleaning are not all made equivalent. That being so, (how) can this simple starting point be used to explore the nature of our understanding of mechanical cleaning?

How Deposits Attach to a Surface

The deposits requiring removal from a surface can be loosely described as particles, where a 'particle' may be anything ranging from a small molecule, through more complex species such as organic, inorganic, and mineral macromolecules, agglomerates and self-organizing structures up to and including a biofilm. The attraction between the particle and a surface will be largely electrostatic in nature but geometric (jigsaw style) interlocking between the micro-morphology of the surface and non-spherical particles will also come into play. There may be furthermore instances where process material has chemically bonded in some way to the surface. This type of 'staining' interaction is not discussed further in this article but some thoughts on the subject have been captured in a poster.[6]

The electrostatic forces between surface and particles operate over a limited length, typically *ca.* 0.3 to 0.6 nm. This implies that larger particles will typically be less strongly bound to the surface than smaller ones, **Figure 3**.

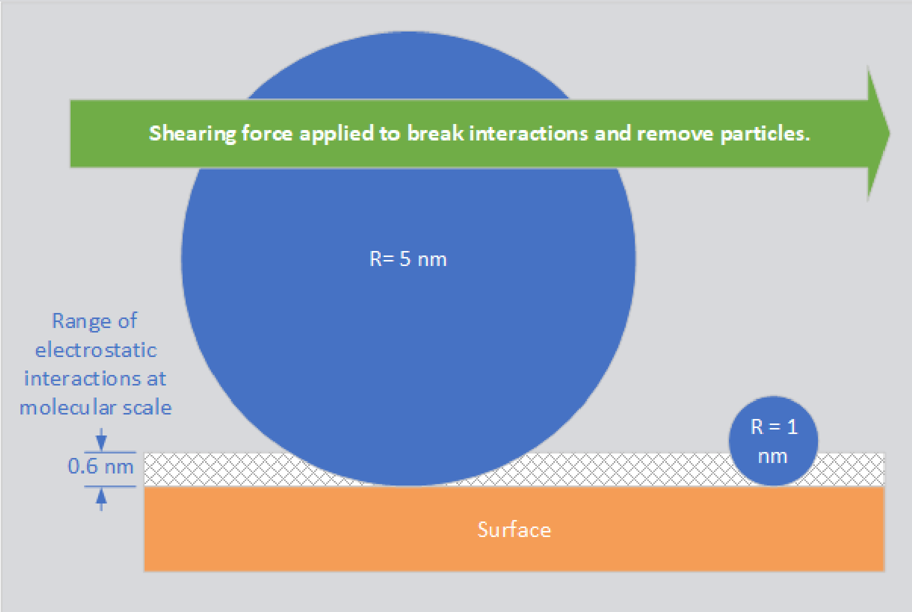

Figure 3 At molecular scale, the attachment force per unit mass decreases with particle size

The reason for this can be appreciated by considering the particles as equivalent spheres. In this case, the proportionality of some important particle characteristics with the length dimension R are as follows.

Particle size (characteristic dimension) α R

Particle volume, mass, and inertia α R^3

Particle surface area α R^2

Particle surface area interaction with surface[†] α R

Since forces acting to detach a particle from a surface will do so via the projected surface area (shear stress), it implies that (in accordance with common experience) large particles will be easier to remove than small ones.

[6] https://www.britest.co.uk/downloads/members_day_posters/2020/sterling_equipment_staining.pdf Accessed 10/07/2020.

[†] The surface area of a spherical cap = $2\pi Rh$. If h is the range of electrostatic interactions on a molecular scale and is assumed constant, then the surface area interaction of the particle with the surface is proportional to R, its characteristic dimension.

A Detailed Look at Pressure Washing

In pressure washing, pressure energy upstream of the nozzle is converted into kinetic energy as the jet is created, and the cleaning action is driven by the high velocity water spray. The specific energy (J/kg) of the spray is given by:

$$\frac{P}{\rho} = \frac{v^2}{2}$$

where P is the pressure (Pa), ρ is the water density (kg/m^3) and $\mathbf{v}$ is the average water velocity (m/s).

A typical domestic pressure washer operates at around 100 bar with a water flow of 360 l/h and electrical power rating of 1400 W. The specific energy of the jet is therefore 10,000 J/kg and the power of the jet is roughly 1000 W (implying 70% efficiency). A typical nozzle will deliver a rectangular footprint, say 10 mm x 2 mm close to the outlet. From this may be determined a maximum kinetic energy flux delivered to the surface to be cleaned of around 50 W/mm^2.

What happens next? In the first instance, since the incident energy is normal to the surface, it is *unlikely* to have much effect on the attractive forces between dirt and surface, however it could certainly crack and reduce to smaller pieces any dirt film (e.g. loose paint on the garage door). Larger, loose particulates will undoubtedly be detached. Some of the energy will be converted to heat through frictional dissipation. It can be shown that for the jet described above, if all the available energy were converted to heat in the water stream then the temperature rise would be just 2.4°C. Some fraction of the energy will be accounted for by the water droplets rebounding from the surface. More significantly, when considering cleaning, much of the water goes into an initially fast-moving thin film of liquid running parallel to the surface. This will lead to a shear stress acting on the surface bound particles, with at least the *potential* capability to overcome the attachment forces and carry the particles away.

We can make an order of magnitude estimate of the shear stress on the particles at a point located on a radius 5 mm from the spray impact. If the depth of the film is 0.5 mm and it comprises 90% of the total water flow (considered an overestimate), then the water velocity will be 11.5 m/s and the power at the edge of the circular film is 5.9 W. This gives a shear stress across the surface of 2 x 10^{-5} N/mm^2. This low value implies that the travelling film will *not* be very effective in detaching dirt particles from the surface, a conclusion which is in accordance with the observation described above.

Analysis of Manual Cleaning

Figure 4 shows a very crude experimental set-up used to estimate the shear stress applied during manual cleaning of the garage door with a wetted sponge.[7] The yellow sponge was weighted down to simulate hand-pressure during cleaning (estimated by pressing down with one hand on a kitchen balance) and was pulled across the surface by a bucket containing just enough water to make the wet sponge move. The total load on the sponge in the image was 1,388 g giving a force normal to the surface of 14 N. The sponge dimensions in contact with the door were 225 mm x 100 mm giving a shear stress of 6 x 10^{-4} N/mm^2. This is an order of magnitude higher than with the pressure washer and consistent with the improved cleaning performance observed.

[7] To watch a brief video see https://www.linkedin.com/posts/john-henderson-6234374_lockdown-ugcPost-6666725259124731904-UyYQ Accessed June 2020

Figure 4 A simple experiment to estimate the drag forces in cleaning a garage door with a wet sponge

Vessel Cleaning in Pharmaceutical Manufacture

Two methods are commonly used for cleaning manufacturing scale process vessels: a spray ball may be inserted to wash down the vessel walls and roof with a solvent (usually water for fire and explosion reasons) or the vessel may be filled with solvent and agitated (perhaps with heating and solvent reflux to clean the roof and overhead lines). The former tends to be confined to gross cleaning only, whilst the latter tends to be the method of choice for rinse checks.

Spray Balls

Sprays balls provide a series of jets oriented in different directions (including upwards) that may or may not traverse the surfaces to be cleaned. The nozzles are too far from the walls for the kinetic energy to be very concentrated. The jets impact the vessel walls and form a liquid film running down the surface to the bottom of the vessel as shown in Figure 5a and this is the primary cleaning mechanism. The first row of Table 2 assesses the cleaning mechanisms acting in this situation. As previously discussed, the pressure of the spray and the velocity of impact (diminished by the distance between the spray ball and vessel wall) are not particularly relevant to cleaning efficiency. It is the thickness and velocity of the falling film of liquid that is key. For a 2 m diameter vessel of ≈ 6,000 L volume, a washing spray of 1,000 Lph will develop into a laminar film of 0.25 mm thickness, running down the wall with an average velocity of 0.17 m/s.

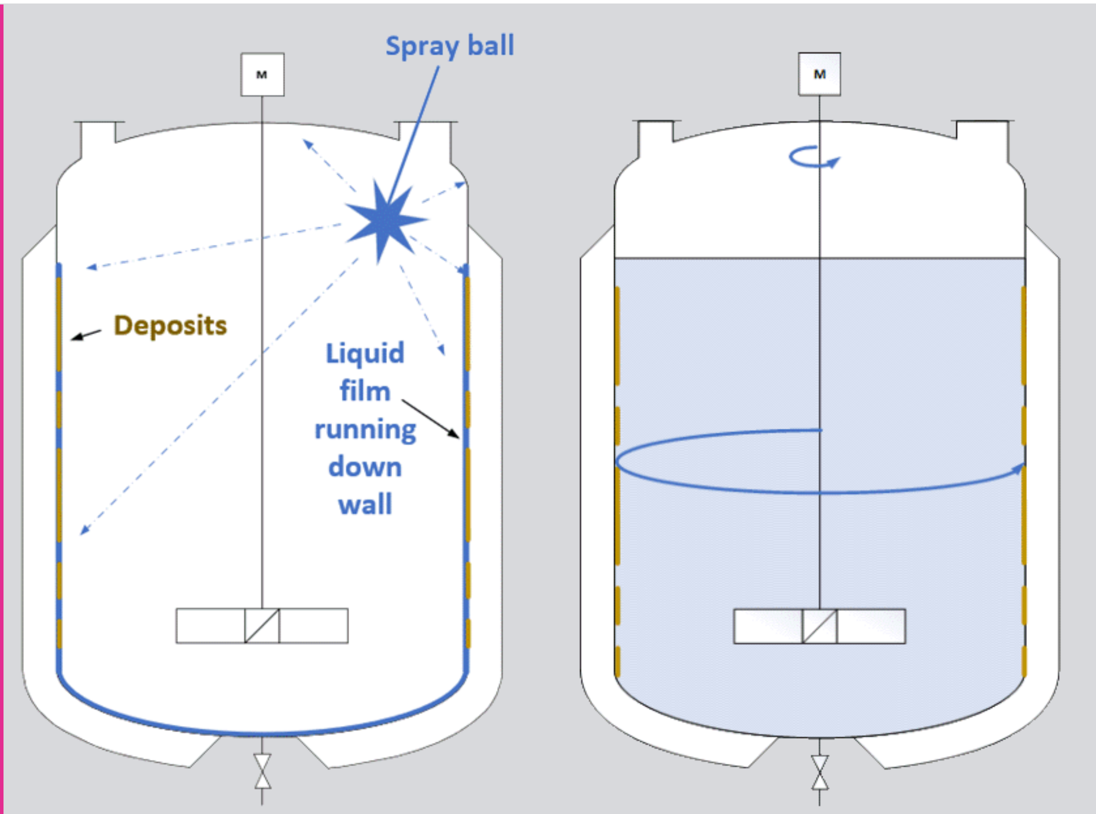

Figure 5 Cleaning a process vessel with, a) a spray ball, and b) by filling with solvent and agitating

Table 2 Driving forces for vessel cleaning

	Time	Temperature	Chemical	Mechanics
Film of liquid flow downwards due to gravity (cleaning vessel using spray ball)	Short to medium contact time	Cold to warm	Detergent in water, water or selected solvent	Low velocity, directed parallel to surface
Cleaning vessel by filling with liquid and starting agitator	Long contact time	Cold to hot (boiling)	Detergent in water, water or selected solvent	Low velocity, directed parallel to surface

Figure 6 illustrates how the film develops as it progresses down the vessel wall and two different cleaning mechanisms are applied to deposits on the wall. Loose particulates will be dislodged and carried away by the shear forces associated with film flow. The shear stress is estimated at 7 x 10^{-13} N/mm^2. At the same time, soluble deposits will dissolve. However, because the flow is laminar, the rate of dissolution will be diffusion limited and therefore slow relative to the available contact time, which is limited to the time taken for the liquid to flow down the wall (believed to be of the order of seconds to a minute). These estimates suggest that this form of cleaning is only likely to be effective for removal of loose, solid deposits in gross cleaning.

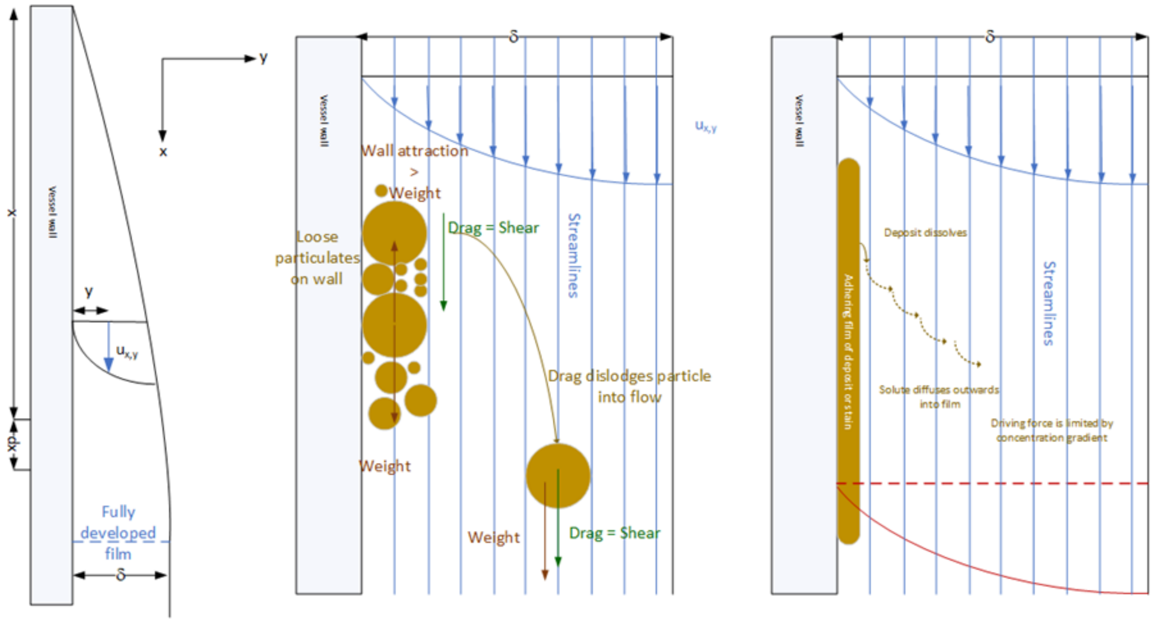

Figure 6 Cleaning effects on vessel wall from falling liquid film

Vessel Filling and Solvent Agitation

Filling the vessel with a selected cleaning fluid and mixing with the agitator, **Figure 5b**, is very frequently used in practice. This method has the advantage of allowing the widest selection of cleaning fluids, however the large volume of solvent required is a disadvantage since this all requires handling, recovery and ultimately disposal. An oft-neglected principle is that the solvent selected should ideally be a good solvent for the material being removed. This is not necessarily the nameplate product produced in the vessel, but rather might be unreacted raw material, an unconverted intermediate, or another impurity residue which might have a different solubility profile to the desired product.

The lower row of **Table 2** describes the driving forces in this form of cleaning. Contact time and temperature are much less constrained than in the previous example. Note however, that the vessel roof will not be contacted at all, unless the cleaning is performed under conditions of solvent reflux.

In any vessel with a volume greater than perhaps a few litres, the flow regime during agitation will be turbulent, the effects of which are visualised in **Figure 7**. Stirring sets up a turbulent shear stress across the wall with an indicative magnitude of the order of 2×10^{-7} N/mm^2 for the same vessel as above. This will be much more effective at removing particulate deposits than the falling film. Turbulence also affects the mass transfer rate for dissolution which will no longer be diffusion limited. In consequence, the dissolution rate increase is estimated to be of the order of 10 to 20 times faster.

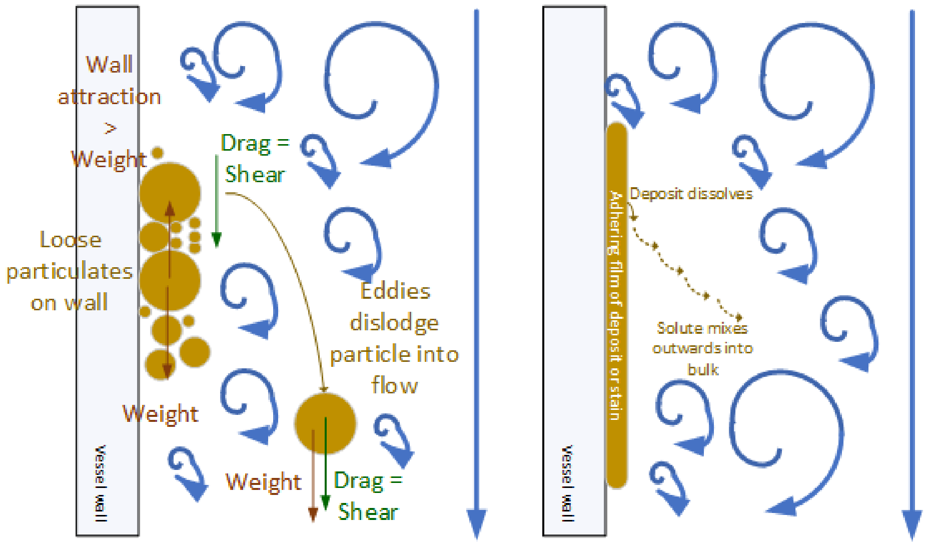

Figure 7 Cleaning effects on vessel wall due to turbulence from vessel agitation

Conclusions

Four different cleaning methods have been described, and the shear forces applied for dislodging particles from the surface to be cleaned have been estimated. These can now be ranked in order of magnitude of the estimated available shear, which ought to correspond to the order of effectiveness of these techniques in removing particulate deposits. The order shown in Table 3 does appear to match empirical observation: in the author's experience changeover teams talk in terms of a hierarchy of cleaning methods from washing down, through filling vessels, to pressure washing with manual cleaning as the last resort.

Table 3 Ranking the four cleaning methods described in order of effectiveness for particle removal

Cleaning Technique	Particulate removal Shear stress (N/mm^2)	Dissolution Effectiveness (Arbitrary rate order factor)	Comments
Manual cleaning	6×10^{-4}	< 10?	Very efficient for small areas but difficult to maintain uniformity across large surfaces.
Pressure washing	2×10^{-5}	< 1?	Has an intense local zone but shear stress drops off rapidly with radius so difficult to maintain uniformity over large areas.
Fill and agitate	2×10^{-7}	10 – 20	Uniform contacting for submerged surfaces only. Vessel mixing is optimised for desired reaction conditions and will not necessarily be optimal for cleaning.
Spray ball/falling film	7×10^{-13}	1	Spray ball appears to be equivalent to multi-point pressure washing. A gravity driven liquid film is the predominant cleaning mechanism. Can reach all parts of vessel but uniformity may be poor for static nozzles and parts of the wall in the shadow of vessel internal fittings.

The main conclusion is that **it is necessary to be more precise in describing the mechanical driver for cleaning in the Sinner's Circle.** For thorough cleaning, what matters is the shear force acting to break the attraction between contaminants and the surface. The mechanical energy needs to be directed *parallel* to the surface being cleaned, which means that many spray and jetting systems which direct energy primarily in the direction perpendicular to the surface may not be as effective as one might imagine at first sight. Perpendicular action will however be effective for cracking up crusts and layers into smaller particles that can then be more readily carried away by the liquid flow. Such systems are therefore best suited to, and often used for, gross cleaning. Even so, applying force in the appropriate direction is like to improve the *rate* of cleaning and perhaps also reduce the total energy and solvent consumption for cleaning.

This analysis also suggests that the key step in chemical (as opposed to physical) cleaning, *i.e.* dissolution *etc.,* is likely to be a relatively slow kinetic processes when acting on a surface. To improve cleaning rates, chemical cleaning needs mechanical assistance. As discussed above, a lateral shearing force to detach particles from the surface is key to success. These findings may provide some insight into the commonly encountered problem of unexpected failures whilst following validated cleaning procedures, an issue which has led to multiple repeated cleaning cycles tending to become a routine part of many turnaround procedures.

For technologists looking to improve the performance of their cleaning procedures, **the message is clear: look for techniques that will apply a shearing force *across* the surface if you wish to improve the rate and completeness of soil removal.**

IT IS NECESSARY TO BE MORE PRECISE IN DESCRIBING THE MECHANICAL DRIVER FOR CLEANING IN THE SINNER'S CIRCLE. THE MESSAGE IS CLEAR: LOOK FOR TECHNIQUES THAT WILL APPLY A SHEARING FORCE ACROSS THE SURFACE IF YOU WISH TO IMPROVE THE RATE AND COMPLETENESS OF SOIL REMOVAL.

Helping organisations gain value from process understanding

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