TELEDYNE | Teledyne LABS

Safety First—Best Practices and Risk Management for Flash Chromatography

keywords: flash chromatography, safety, solvents

Summary

Flash chromatography is a popular purification technique that, when performed correctly, is fast, easy, and safe. To ensure its continued safety, you must be aware of hazards arising from using chromatography media and solvents.[1]

What are the issues?

Any chemicals handled in the lab come with their own unique risks. Flash chromatography often employs relatively large amounts of solvents, whose risks to varying degrees include spill, fire, and chemical exposure. Whenever solvents are used for any application, solvent vapors in the atmosphere can ignite.

What should we do?

Fortunately, safety incidents are preventable. As a first line of defense, automated flash chromatography systems—such as the Combi*Flash* NextGen—have features that can detect organic vapors and prevent spills and bursts. Furthermore, excessive vapors, electrostatic charging, and sparking can be prevented with appropriate equipment and procedures.

The nature of flash chromatography hazards

Media

When performing manual flash chromatography, exposure to silica or solvent is possible when making silica gel slurry or filling columns.[2] Avoid exposure silica dust is a skin, eye, and respiratory irritant. (However, silica gel lacks crystalline silica and its associated risks).[3] Exposure is also a risk when disposing of column media once your run is complete.

Automated systems use columns in the form of cartridges that are prepacked with media, thus limiting your exposure to it and to any compounds adsorbed onto the media. An air purge function removes solvent from these cartridges before disposal—that is, before further handling.

Broken glass

Traditional flash chromatography moves material through glass joints, adapters, and columns using pressured gas. If the glass were to fail under pressure, you could be cut by it.[4]

Automated systems, however, use plastic column bodies that eliminate glass laceration risk completely. Furthermore, plastic has a much higher tolerance to pressure than glass. Columns offered by Teledyne LABS have machine welded end fittings, which strengthens them to prevent leakage and to minimize possible exposure.

Solvent exposure

Solvent exposure during flash chromatography is the main hazard due to the nature of solvents and because there are several avenues for it. Solvent exposure during column packing has already been discussed. Exposure is also possible when refilling the solvent containers (or when filling the glass column with solvent while doing manual chromatography) and when collecting fractions off the column or combining fractions for evaporation. Another means of exposure is by column failure due to pressure burst.[5] An additional source of chemical exposure risk is from the mixture of compounds undergoing separation from the crude product, which is similar to risks during synthesis, post-chromatography work-up, and characterization.[6] Risks of exposure vary with the solvent; these include toxicity and flammability.

Automated systems employ several means to minimize solvent exposure.

- Systems use pumps to deliver solvent to the column; systems with vapor sensors can detect potential leaks, stopping flow to the system and minimizing the volume of solvent spilled. Since there isn't a gravity- or air-driven solvent reservoir above the column, less solvent is spilled.
- Systems pump out of capped bottles and mix the solvent automatically. The ability to perform gradients decrease the amount of time and solvent necessary to complete the separation compared to manual chromatography.
- New method development tools like PeakTrak's Focus Gradient Generator allow for further optimized methods that minimize the length of the run and decrease the amount of solvent needed.
- Waste level sensing stops the instrument before it overfills the waste container.
- RFID-labeled racks ensure that the correct tube and rack layout is selected so that fraction collection doesn't miss the tube or overfill it.
- And, optionally, a vapor enclosure can connect the internal fraction collection area to an exhaust source.

Bursting

The University of Wisconsin-Madison's flash column chromatography *Safety Guideline* states that "the major safety concern for flash chromatography is possible bursting due to excess pressure build up inside the system."[7] Such an event makes exposure to compounds, silica media, and solvents possible.

Automated flash chromatography systems reduce the possibility of bursting. They have built-in pressure sensors to monitor column pressure, and they use columns that store flow rate and pressure limits using RFID tags. These sensors and tags inform the system to load appropriate flow rate and pressure limits for its columns.

Furthermore, plastic columns have a much higher tolerance to pressure than glass. Columns offered by Teledyne LABS have machine welded end fittings, which strengthens them to prevent leakage and minimize the possibility of exposure. Some columns offered by other suppliers may not be welded and have screw cap fittings, which creates a higher likelihood of leaking at this critical joint.

Solvent flammability

Organic solvents used in flash chromatography and their vapors can be flammable at the right temperatures and in the right concentrations, given an ignition source.

The *Flammability Guide from the European Solvents Industry Group* (referred to hereafter as the "*Flammability Guide*") provides much useful information about solvents, fluid flow, and static electricity charging. The following discussion is informed by—and will frequently refer to—that document.

Flammability risk

The *Flammability Guide* (section 2.2) lists three factors that must be present to create a fire or explosion risk

1. **The presence of a sufficient oxidizer.** This is usually oxygen from the air. This isn't really a controllable factor—of course it's not practical to remove it under normal circumstances! However, oxygen displacement can be a practical approach to stop a fire.
2. **Flammable solvent vapor concentration,** either separately or together, can create a hazard. These can be controlled. The following two metrics indicate hazardous conditions:
   - The *flammable range* (or explosive range) is "the range of vapour concentrations in air that can undergo combustion" if ignited.[8] The flammable range is bounded by its lower explosion limit (LEL). Vapors must be kept well below that limit.
3. The *flash point* is "approximately the lowest measured temperature at which the solvent can produce vapor concentrations within the Flammable Range at atmospheric pressure."[9] Solvents with higher flash points have correspondingly higher explosion level limits.

An ignition source can ignite flammable mixtures of solvent vapors and air.

Flammability and explosion risk is reduced by controlling environmental temperatures, solvent vapor concentrations, and by controlling or keeping sources of ignition away from these environments. Temperature and vapor control recommendations below are adapted from the *Flammability Guide*, section 1.3.

Controlling temperature

Control flammability risk by controlling the temperature of both the solvent and the surrounding air:

- Be mindful of the solvent's flash point. Its temperature should be kept below that point by an appropriate margin of safety (5 °C or 15 °C, depending on the solvent and other factors) when practical; however, many solvents used for flash chromatography have flash points that are well within temperatures of normal use, which means that control of vapor concentration is critical to use these solvents safely. Other things to keep in mind:
  - The flash point only establishes the temperature to which a liquid is heated in a specified (experimental) apparatus before a flame will form when a source of ignition is present.
  - The ventilation and the size of the environment are other factors that contribute to vapor concentration levels.
  - Fortunately, temperature and ventilation can be controlled with appropriate measures. This is what allows chemists to regularly use low flash point solvents like hexane or ethyl acetate safely.
- The air and solvent mixture must be kept below the autoignition temperature—the temperature at which the mixture could auto ignite (i.e., without an external source of ignition). The operating temperature should be kept well below this.

A solvent's flash point and autoignition temperature will be indicated in the Safety Data Sheet (SDS) provided by your supplier.

Controlling vapor levels

Ensure that ventilation is adequate:

- "Vapors need to be diluted to well below the LEL to ensure safe operation. A level of <25% is often specified."[10] Why "well below?" First, the occupational exposure limit could be even lower than the LEL. Also, the LEL is a theoretical limit—the actual limit might be lower. Consequently, a margin of safety below the LEL is needed.
- To ensure adequate ventilation, a mechanical ventilation system may be necessary. It should provide six air changes per hour.

As with its flash point and autoignition temperature, a solvent's lower and upper explosion limits will be indicated in the SDS provided by your supplier.

Combi*Flash* flash chromatography systems have internal vapor sensors to monitor the organic vapor levels inside the instrument to help detect internal leaks and prevent hazardous conditions by keeping levels well below that lower explosion limit. This vapor sensor doesn't replace the need to place the system in an adequately ventilated environment, as it is not intended to detect leaks or solvent vapor sources external to the system. The sensor works by detecting vapors present inside the system. When vapor levels are excessive, the system will stop the pumps.

Combi*Flash* NextGen Vapor Limits

Sensitivity Setting	Percentage (relative to the LEL of hexane)
Low	45%
Medium	15%
High	5%

Currently, all Teledyne LABS Combi*Flash* chromatography systems have this vapor limit feature.

Controlling ignition risks

The *Flammability Guide* (section 2.5) lists several ignition sources that could be found in a laboratory, including open flames and smoldering (e.g., from matches or gas burners), hot surfaces (e.g., ovens, furnaces, lasers), sparks (electrical or mechanically produced), and electrical discharges. Perhaps easily overlooked are solvents in rags, filters, etc. These can self-heat from chemical reactions and create an ignition source.

Electrical discharges include those from motors, switches, fuses, extension cords and—less obviously—from calculators, cell phones, and flashlights. Inadvertent ground loops can be a source of discharge.

But static electricity is the most important and common accidental ignition source.[11] Static charge can accumulate in the solvent itself and create conditions for a potential spark. This process, and the means of controlling it, will be explained in detail below.

Electrostatic hazards and flash chromatography

As noted earlier, static electricity is the most common accidental solvent ignition source. Static electricity is an imbalance between positive and negative charge within a material. You can generate it during ordinary activities including walking on carpet in your fleece pajamas with covered feet, rubbing a balloon on your head, and removing cling wrap from a package or container. You probably wouldn't do any of these in your laboratory, right?

Or would you? In the lab, you might walk across a carpet with rubber-soled shoes, idly comb your hair, or remove plastic wrap from new equipment.

Furthermore, static electricity can arise from solvent handling, liquid flow, stirring, agitation, or mixing. The main concern for static electricity generation in flash chromatography is charging by liquid flow.[12] Refer to the *Flammability Guide*, section 3.2, from which the following discussion is adapted.

How solvents become charged

Charge accumulation and dissipation

Solvent pumping and pipe flow—especially turbulent flow at high velocities—are important sources of electrostatic charging during flash chromatography. This can be further aggravated if the liquid passes through a fine filter or contains suspended particles or other immiscible matter.

The amount of charge generated increases proportionately to the linear velocity of the solvent. This makes the choice of system so important for your process. Systems should be designed to use an appropriately sized tubing diameter to ensure that linear velocity doesn't increase drastically as flow rates increase. The Combi*Flash* Torrent, for example, uses much wider tubing than the Combi*Flash* NextGen, allowing it to safely go up to 1 L/min.

However, while static builds up within a liquid, it also dissipates—continually leaks—to the walls of its container (or tubing). Fast dissipation is desirable because it prevents hazardous voltage differences between the solvent and the walls of its container. How quickly the solvent charge can dissipate to ground depends on the material of the container or tubing (stainless steel or plastics) and the conductivity of the solvent.

Tubing materials

Most non-metallic tubing is non-conductive; it doesn't allow the efficient transfer of charge from the motion of the fluid to dissipate to the tubing and ground to the atmosphere. This results in the accumulation of static charge and presents a risk.

The use of special static dissipative tubing on Teledyne Combi*Flash* systems allows the charge generated by the fluid to be transferred to the tubing surface, dissipates it to ground through the instrument or through moisture in the air, and prevents it from accumulating a large charge potential.

High and low conductivity solvents

The rate at which dissipation occurs in a solvent depends in great part on its conductivity. Charge dissipates quickly from a solvent with higher electrical conductivity, while a low-conductivity (i.e., ≤50 pS/m) liquid may take several seconds to lose most of its charge. Generally, "hydrocarbon solvents usually have low conductivity whilst most polar solvents (e.g. many oxygenated solvents such as alcohols) have high conductivity."[13] The *Flammability Guide*, p. 21, has a useful table of common solvents and their conductivities; the following list is similar:

Substance	Conductivity pS/m	Dielectric constant	Relaxation times s
Acetone	6×10^6	21	3.1×10^{-5}
Isopropanol	2×10^6	18	8.1×10^{-5}
Ethyl Acetate	2×10^6	6.2	2.8×10^{-5}
Ethanol	4×10^6	25	5.6×10^{-5}
Methanol	7×10^6	33	4.2×10^{-5}
n-Heptane	4	1.9	4.3
n-Hexane	24	1.9	0.71
n-Octane	9	1.9	1.9
Toluene	5	2.4	4.3
n-Pentane	24	1.8	0.68
m-Xylene	9	2.4	2.4

Adapted from *Flammability Guide - Best Practice Guidelines for Safe Handling of Flammable Solvents*; European Solvents Industry Group (ESIG): Brussels, June 2013, p. 21.

But don't let the choice of a higher conductivity solvent make you complacent: electrostatic charge can accumulate in medium- or even high-conductivity solvents during certain operations.[14] This is why good instrument design is critical for safe operation for all solvents used in flash chromatography.

Furthermore, even some high-conductivity materials have an elevated risk of ignition: "Ethyl acetate has been associated with a number of electrostatic ignition incidents and even though it has a high conductivity, it should be treated as a low conductivity material. It would be prudent to treat other light esters similarly."[15]

Effect of humidity levels on static electricity

Although humidity isn't discussed in the *Flammability Guide*, the lack of it can create hazardous conditions because dry air facilitates the transfer and accumulation of static electricity instead of allowing it to dissipate. Dissipation from solvents is aided by humidity in the air because the particulate matter in the water vapor gives surface charge someplace else to go and allows electrostatic charge to dissipate from surfaces. Dryer air doesn't do this as well. If the air is especially dry, even walking across a carpet can generate an enormous static charge.[16] Increasing the humidity in the air can prevent this.

You may notice the laboratory humidity can vary greatly; the success of a moisture sensitive reaction could depend on the season. For example, humid Nebraska summers aren't ideal for Grignard reactions, but during the cold dry winters they work splendidly. Your laboratory environment may vary depending on its location and on the time of year. A laboratory in a tropical region might be expected to have more humid air than one in a colder region. However, a heavily air-conditioned laboratory might have dry air year-round in either location if it is not humidified.

Ultimately, a 5% swing in humidity could be the difference in generating an amount of static electric charge on ungrounded, non-conductive tubing to create a potential hazard situation. Proper system design, grounding, and the use of static dissipative tubing take the guesswork out of varying laboratory humidity levels.

Controlling static electricity

Refer to the *Flammability Guide*, section 3.3, for static control measures for solvents. Measures from this document are summarized below.

Grounding

Adequately ground equipment.

- Ground all conductive system components to prevent sparking. The path to earth should have a resistance of <10 Ω.
- Regularly verify that equipment complies with earth resistance requirements and that conductive or dissipative hoses meet end-to-end resistance requirements. Combi*Flash* systems are designed with a static-dissipative black tubing. This tubing is unique to Teledyne chromatography systems.
- Ground your solvent and waste bottles during operations when pumping from or into a container, when filling, or when emptying a container. Also, be sure to ground yourself during any of these operations.

Personal protective equipment

Electrostatic dissipative gloves and footwear should be worn; flooring should be dissipative as well. If dissipative gloves do not offer sufficient hand protection for an operation in other respects, that operation should be re-evaluated to avoid material handling or to ensure proper grounding of items carried by the operator.

Operating procedures

Design operating procedures to reduce turbulence, velocity, and splashing of solvents.

- **Keep conductive materials out of tanks** with properly designed operating procedures and clothing.

Be patient when filling, dipping, or otherwise handling solvents. (These are discussed in the *Flammability Guide*, section 1.3)

- **Wait.** Give charge time to dissipate.
- **Avoid splash filling.** Dip pipes or bottom filling should be used for flammable, low-conductivity solvents.

Know your solvent containment system.

- **Avoid non-conductive or non-dissipative plastic containers.** "Do not fill solvents into any insulating plastic containers or tanks [greater than 5 L] unless the [flash point] of all solvents handled in the vicinity is >60 °C."[17]

References

Column Chromatography; University of Massachusetts: Amherst, n.d. https://ehs.umass.edu/sites/default/files/Column%20Chromatography_2.pdf (accessed August 5, 2024)

Standard operating procedure: Flash column chromatography; University of Wisconsin- Madison, n.d. https://safety.engr.wisc.edu/wp-content/uploads/sites/706/2018/07/Flash-Column-Chromatography-SOP-15.pdf (accessed August 5, 2024), citing http://www.ehs.berkeley.edu/sites/default/files/lines-of-services/workplace-safety/51silicagel.pdf.

Industrial Humidity Control: Controlling Electrostatic Discharge in Electronics Manufacturing; n.d. Microcool https://microcool.com/industrial-humidity-control-controlling-electrostatic-discharge-in-electronics-manufacturing/ (accessed August 5, 2024).

Flammability Guide - Best Practice Guidelines for Safe Handling of Flammable Solvents; European Solvents Industry Group (ESIG): Brussels, June 2013. https://www.esig.org/wp-content/uploads/2018/03/170914_BPG_Flammability_Final-002.pdf (accessed August 5, 2024).

Endnotes

1. *Column Chromatography*; University of Massachusetts Amherst, n.d. https://ehs.umass.edu/sites/default/files/Column%20Chromatography_2.pdf (accessed August 5, 2024) p 2.
2. *Standard operating procedure*: Flash column chromatography; University of Wisconsin- Madison, n.d. https://safety.engr.wisc.edu/wp-content/uploads/sites/706/2018/07/Flash-Column-Chromatography-SOP-15.pdf (accessed August 5, 2024), citing http://www.ehs.berkeley.edu/sites/default/files/lines-of-services/workplace-safety/51silicagel.pdf. p 4.
3. Univ. of Massachusetts, p 2.
4. Univ. of Massachusetts, p 2.
5. Univ. of Wisconsin, p 4.
6. Univ. of Wisconsin, p 4.
7. Univ. of Wisconsin, p 4.
8. *Flammability Guide - Best Practice Guidelines for Safe Handling of Flammable Solvents*; European Solvents Industry Group (ESIG): Brussels, June 2013. https://www.esig.org/wp-content/uploads/2018/03/170914_BPG_Flammability_Final-002.pdf (accessed August 5, 2024).p 12.
9. ESIG, p 12.
10. ESIG, p 12.
11. ESIG, pp. 8, 17.
12. ESIG, p 19.
13. ESIG, p 8.
14. ESIG, p 8.
15. ESIG, p 8.
16. Industrial Humidity Control: Controlling Electrostatic Discharge in Electronics Manufacturing; MicroCool. https://microcool.com/industrial-humidity-control-controlling-electrostatic-discharge-in-electronics-manufacturing/ (accessed August 5, 2024).
17. ESIG, pp 9-10.