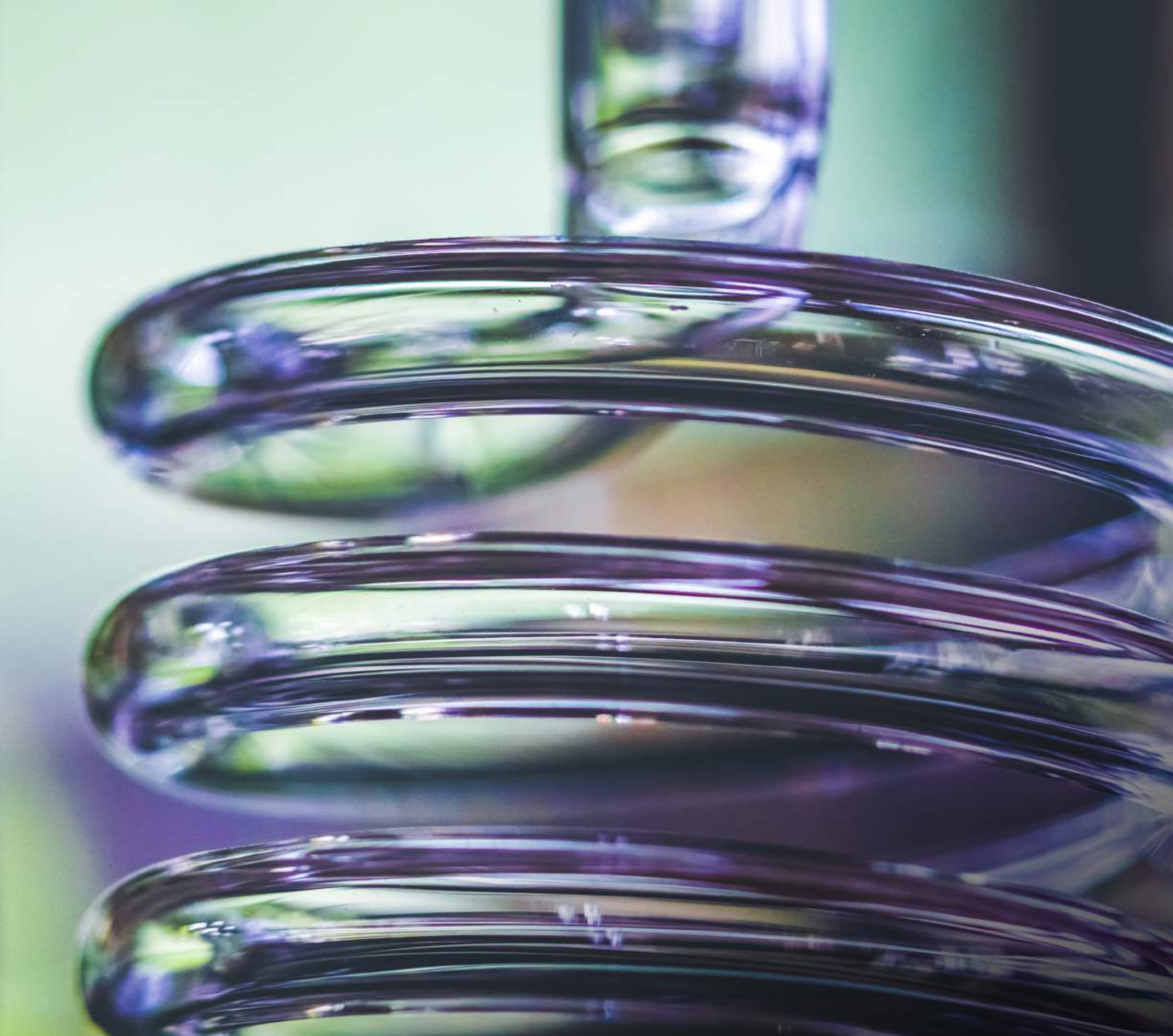

The Importance of Liquid Temperature Control

in Drug Discovery and Development

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TEMPERATURE CONTROL

Consider this...

You wake up in the middle of the night, drenched with sweat, and kick off the blanket – feeling like a heat-generating furnace for an industrial process. Your body has enacted part of its defense mechanism to combat infections by raising your temperature. Infectious agents, such as viruses or bacteria, reproduce best at normal body temperature. By generating a fever, elevated body temperature, the human body can combat infection by raising the temperature above ideal microbial reproduction. Obviously, not all illnesses induce a fever, but to develop medications to combat and treat ailments, temperature matters greatly.

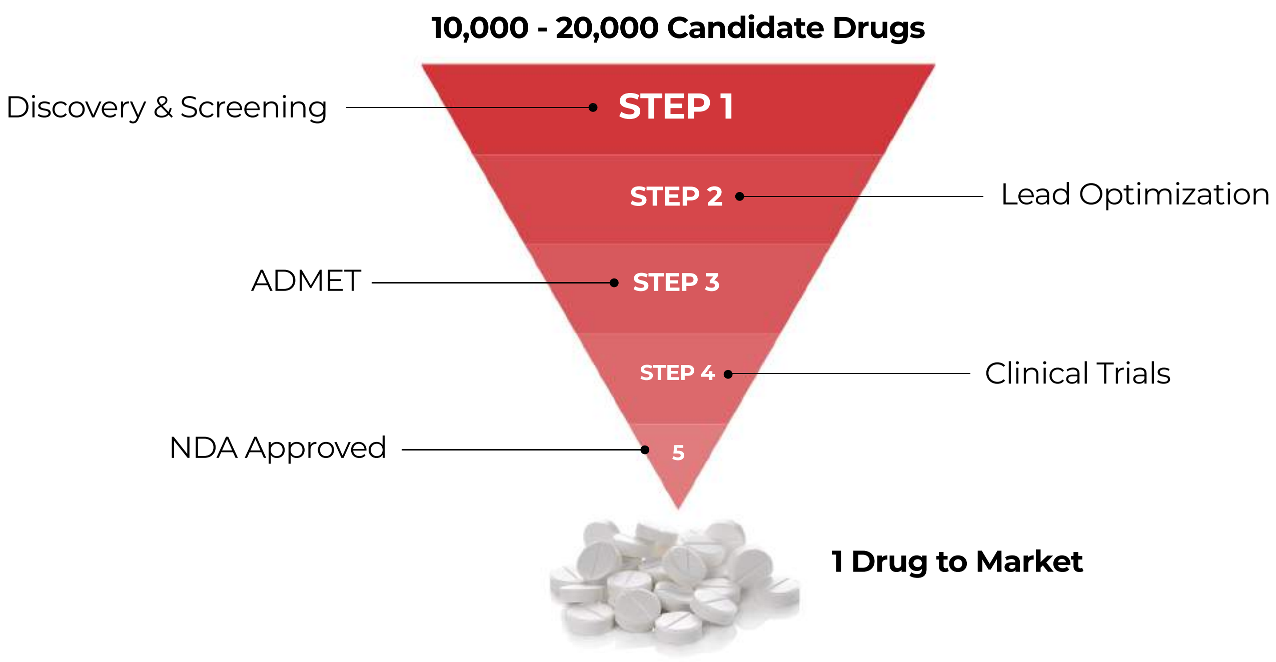
In this document

Overview

The course of bringing a drug to market spans a wide variety of scientific endeavors to discover, screen, formulate, test in the clinic, and scale-up for production. Regardless of whether the final active pharmaceutical ingredient (API) formulation is ingestible, injectable, topical/transdermal, or inhaled, temperature plays a crucial role along the way. Equipping labs with the appropriate liquid temperature control units (TCUs) to provide adequate heating and/or cooling facilitates faster and repeatable results. TCUs equipped with data-logging and real time monitoring via IoT (Internet of Things) greatly enhance scientists' ability to respond quickly to demands and track data in the current fast-paced R&D environment. This document will review how TCUs impact the various stages of API development, calculation tools, future trends, and maintenance.

Developing active pharmaceutical entities starts with the discovery of a therapeutic molecule. These molecules derive from targeted synthesis conducted on a small scale or isolated from biological sources and then screened. For the chemical synthesis of the target molecule, a synthetic route is developed to produce quantities for various in vitro or in vivo studies. Typically, small scale synthesis and time constraints dictate synthesizing enough of the molecule to support screening efforts, regardless of cost. Chemists use a variety of apparatus to synthesize these target molecules. Regardless of the vessel size, temperature plays a vital role in conducting these molecular transformations and purifications. As the testing progresses into human trials, the required drug quantity increases, thus transitioning synthesis into the kilo lab, pilot plant, and eventually into production facilities. Optimization of the synthetic route as the scale increases places extreme importance on temperature control for yield, purity, safety, and batch-to-batch reproducibility.

The Drug Discovery Process



The onset of the SARS-CoV-2 pandemic exemplifies the unprecedented need for fast candidate discovery, scale-up, and clinical testing. The global 'all hands on deck' situation applies to the development of small molecules and biological treatments, such as antibodies, vaccines, and mRNA therapies.

Temperature in Synthesis

Temperature control plays a critical role in organic chemistry transformations. Whether using dry ice/acetone, heated stir plates, heating mantles, or jacketed reactors with a TCU, chemists rely on temperature to facilitate synthetic processes. Scientists balance multiple factors to determine the correct temperature to yield the desired product. At cold temperatures, the use of vigorous reagents can be controlled more easily, and, in some cases, the correct temperature can reduce or eliminate unwanted side products. From a reaction rate perspective, a typical rule of thumb states that an increase of 10°C doubles the reaction rate. In small scale synthesis, the effect of heat flow is typically not an issue as any exotherms are easily handled by a dry ice/acetone bath or small jacketed flask connected to a recirculating chiller. The use of external temperature probes to monitor and control the temperature from inside the vessel ensures reliable set points and data capture where it matters.

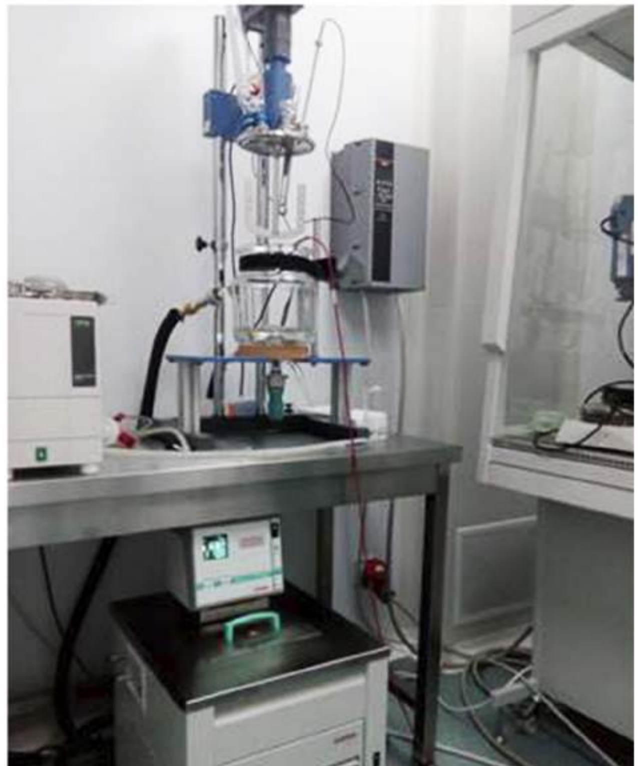
As the drug development process progresses, it requires larger amounts of API. The increase in scale warrants synthetic route and purification optimization from two perspectives: cost and safety.

Cost: Route optimization seeks to lower total synthesis/purification cost by optimizing conditions to increase yield and seek alternate synthetic strategies to reduce or replace expensive reagents or eliminate reaction/process steps. Temperature plays a role in the route optimization strategy. In the discovery labs, the medicinal chemist might have developed a synthesis utilizing dry/ice acetone (-78°C) to perform a reaction. If the drug proceeds to market with a projected demand of hundreds of kilograms per year, scaling up a -78°C process to a ≥100 L reactor could be cost-prohibitive. Process chemists work to optimize the conditions under more economical temperatures for scale-up and production. This could involve a different synthetic route at warmer temperatures more conducive to larger-scale applications.

Safety: Scaling chemical processes requires extensive safety assessments and evaluation. Dealing with an exothermic reaction in a 100 mL glass reactor is relatively easy to control and contain. Scaling that reaction up to a 100 L reactor could result in a runaway situation leading to a lost batch, equipment damage, and potential personnel injury. A thorough understanding of reaction thermodynamics is needed to scale up a process safely, typically via the use of reaction calorimeters to determine heat flow values. Determining the heat flow values in a controlled calorimeter environment enables chemists and engineers to understand key parameters of a reaction/process and assess the feasibility of scaling up.

Temperature in Synthesis (continued...)

Reaction calorimeters vary in methodology and scale. Some smaller reaction calorimeter products (1L vessel size and smaller) utilize Peltier technology for temperature control. Supplementing these with a recirculating chiller can achieve reaction conditions ≤ -20°C. Other methods rely on jacketed vessels monitoring internal reactor temperature and jacket temperatures. The heat balance approach, $Q = m_c \times C_p \times (T_o - T_i) + Q_{losses}$; Q = heat transfer (W), m_c = mass flow of jacket fluid (kg/s); T_o = outlet jacket fluid temperature; T_i = inlet jacket fluid temperature; Q_{losses} = environmental losses (W). Using a temperature control unit equipped with in-line temperature sensors (at reactor inlet/outlet) with a mass flowmeter, provides an easy method to screen reactions at various scales and gather calorimetric data simultaneously. This can lighten the developmental bottleneck of running all processes through a dedicated calorimeter. Heat flow calorimeters remain the most popular technique where $Q = U \times A \times (T^r - T_j)$. Q = heat transfer (W), U = heat transfer coefficient (W/m^2 K); A = heat transfer area (m^2); T_r = reaction temperature; T_j = reactor jacket temperature. This procedure requires calibration to determine U and A values. TCUs provide the reactor jacket temperature control or supplement an internal jacket fluid loop by providing sub-ambient cooling as needed. Typically, the operation of reaction calorimeters requires an expert user.


JULABO FP50 Refrigerated/Heating Circulator and 2L Reactor

If the reaction heat output is known (whether an exotherm or endotherm), it is possible to calculate the necessary TCU heating or cooling power with various calculation tools. By knowing the contents and heat transfer fluid volumes, desired temperature change, time to temperature, and heat output of the process, a heating or cooling power value can be determined. Adding a capacity safety factor of 25% will account for process losses and provide a suitable TCU power value for the application.

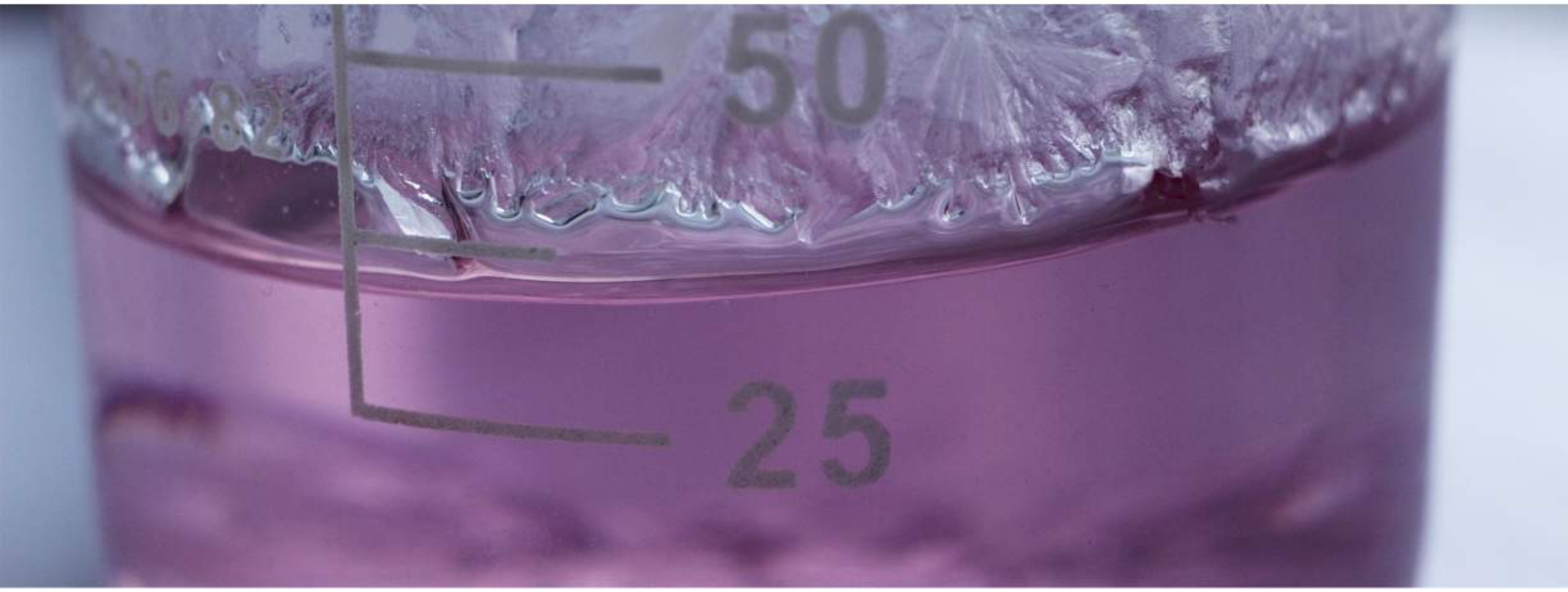
An example of a handy calculator to determine the value is available from JULABO USA, Inc. and can be found on the Julabo US App (available in the Apple Store and through Google Play).

In addition, a hazard safety analysis covers a broad range of "what if" scenarios and how to address them: examples could include too much reagent added, temperature set too high, and an addition rate that's too fast. Additionally, crystallization purification techniques analyzed via calorimetry determine the heat absorbed by the process. This data proves useful in measuring and optimizing the crystallization process.

Go with the Flow

To this point, all prior workflows in this document focused on batch processes. Over the past 20 years, flow chemistry has matured to the point where medicinal and process chemistry departments use this technique to develop chemistries not possible in traditional reactor systems. The FDA remains supportive of API synthesis via continuous manufacturing, due largely to improved quality control.[1] Continuous flow processing affords increased synthetic capabilities due to lower reaction volumes, high pressure operation ability, and better temperature control. These capabilities open options for the use of energetic and challenging reactions safely, even integrating post-reaction work-up and/or purification within a small footprint. The increased pressure and mixing via diffusion provide distinct advantages over traditional batch protocols. From a temperature perspective, since the flow channels have such a high surface area-to-volume ratio, instant temperature changes can be affected by pre-set temperature zones. Given the high surface area-to-volume ratio of the technique, these temperature zones can utilize smaller capacity TCUs to provide the appropriate heating or cooling zones. Additionally, temperature adjustment proceeds quickly to facilitate reaction optimization investigations, thus saving development time. The use of flow chemistry with added safety, smaller footprint, and lower capacity TCUs, can save organizations capital and operational expenditures.

1. https://www.outsourcing-pharma.com/Article/2015/05/01/FDA-calls-on-manufacturers-to-begin-switch-from-batch-to-continuous-production



Crystallization Studies

Product isolation and purification techniques can add significantly to production costs. Distillation and crystallization remain much more economically appealing than chromatographic purification or other methods. Crystalline forms of APIs can exhibit different chemical properties that affect a variety of parameters, including solubility, bioavailability, dissolution rate, stability, etc. Polymorph studies must be conducted to determine the forms and how they affect drug efficacy or safety. If an API has stability or solubility issues, then researchers might investigate screening for salt or cocrystal forms.

Crystallization Studies (continued...)

Many input properties and process parameters come into play, depending on the type of crystallization. The basis for crystal formation and growth is the reduction of solute solubility, whether initiated via cooling, evaporation, antisolvent addition, or reaction (precipitation). Temperature control plays a vital role in all methods by first warming a solution to create a saturated or supersaturated mixture. Crystallization via cooling requires carefully controlled temperature reduction over time to initiate and promote crystal growth. Evaporation can require increasing the temperature to remove the solvent either at atmospheric conditions or under reduced pressure. In these applications, a jacketed vessel or filter reactor connected to a TCU facilitates the crystallization process.

Distillation

Distillation techniques developed historically, to large extent, by alchemists. Today's distillation equipment is far more modern, but the importance of distillation remains vital to chemical processing. Distillation enables the separation of components based upon boiling points. The proliferation of the rotary evaporator in the organic chemistry workflow has rendered it a ubiquitous tool on every lab bench and within the kilo lab. Temperature plays a vital role in effective rotary evaporation: by warming the solution in the rotating vessel, setting a recirculating chiller controlling the condenser(s) to 20°C, and adjusting the vacuum to render the solvent vapor at 40°C. Maintaining a 20°C ΔT between the solvent vapor temperature and condenser temperature yields efficient vapor condensation. Some general guidelines include the 20/40/60 or 10/30/50 rules where the condenser temperature set point is 20°C/10°C with a bath temperature of 60°C/50°C and adjustment of the vacuum to yield a solvent vapor temperature of 40°C/30°C.

Distillation (continued...)

Vacuum distillation for solvent removal from reactors follows similar protocols. Sizing the cooling power of the condenser chiller remains a critical factor for successful solvent evaporation. If the evaporation rate exceeds the cooling capacity of the chiller on the condenser, then the solvent vapor will exit via the vacuum pump. This could lead to a premature failure of the vacuum system and the release of volatile components to the atmosphere. The basic tenets discussed for rotary evaporation also apply to other distillation methods such as short path, fractional, wiped/rolled film, and rising/falling film systems. Temperature optimization of the heated zones (evaporation bodies and/or feed tanks and piping for viscous materials) and cool zones (condensers and vacuum traps) with vacuum setting and feed rate (as appropriate) result in efficient and reproducible isolation of desired components. Properly sizing the TCUs for heating and cooling capacities and temperature ranges remains critical to the distillation unit operation and maximizing throughput.

Formulation

Formulation of the API into solid, liquid, dermal, or inhalation dosage forms provides assurance that the proper amount of drug delivers to the patient. This encompasses testing to ensure that the drug remains stable, determination of the expiration date, and for solid forms, how well the formulation dissolves in the digestive system. Automated dissolution testing systems utilize a heating circulator to control the test at 37°C. Capsules, tablets, or pills placed in the device mimic the actions of the stomach with water or dilute HCl solutions.

Scale-up: Things to Look for from TCU Manufacturers

Once a drug candidate progresses into Stage 3 and beyond, the process parameters for synthesis, purification, and formulation have been well defined. At this point, GMP/cGMP practices come into play to validate the procedures and equipment used therein. IQ/OQ documentation from the TCU manufacturer facilitates the validation process. As the scale increases, so does the use of automation, typically via Programmable Logic Controllers (PLCs). Implementation of automation to control process variables minimizes batch to batch variability, reduces exposure to operators, and increases productivity. Any TCUs used should have a variety of I/O capabilities, including digital or analog to integrate with the PLC platform.

JULABO PRESTO W91 and 100L Reactor

Time equals money, making minimization of downtime a priority. TCU warranty, maintenance/service plans, and support-by-phone play important factors in reducing downtime. The cost of a TCU service plan can pay dividends compared to the revenue lost from production stoppage. The addition of augmented reality and virtual service, as well as annual fluid analysis and testing can also greatly reduce potential interruptions. Additionally, the emergence of IoT technology implemented in a TCU provides 24/7 monitoring capability. With this technology, the TCU manufacturer has access to the systems' functional data to assess its performance. Performance data can help identify potential issues, allowing TCU service providers to address them before a failure occurs. If a TCU error does occur, the IoT technology captures the incident, leading to quick remediation of the problem.

Conclusion

Temperature control plays a pivotal role in the pharmaceutical industry, encompassing everything from initial discovery to final production and formulation. This applies to all APIs ranging from small molecular entities to large biological moieties. Over the past few years, research has shown an increase in the development of biological drug entities. However, small-molecule research has its place and continues to grow also. Organic synthesis parameters tend to be more extreme from a temperature range based upon the needed chemical transformation(s). The saying "use the proper tool for the job" applies directly to laboratory and production unit operations. It is highly recommended to consult with the TCU manufacturer. With a thorough understanding of the process and any important related parameters, consultation with a TCU representative can provide instrument options to achieve the desired temperature control for the procedure. Using and maintaining properly sized TCUs, including chillers, heating circulators, and refrigerated/heating circulators, ensures reliability, reproducibility, and flexibility for research, scale-up, and production of APIs.

For more information visit: **https://www.julabo.us**

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