Drug Discovery Advances Inextricably Linked to Specialty Gases

An Applications Report from Linde Gases

Both the pharmaceutical and biotech industries are heavily dependent on gases, from high purity gases for laboratory use, to process gases for production processes such as chemical synthesis, sterilization gases, and gas mixtures to grow biological cultures.

The development and commercialization of new medical drugs is a complex and costly process and the pharmaceutical industry continues to demand ever more advanced products. The process of drug discovery revolves around identifying one molecule among millions of candidate molecules, followed by synthesis, characterization, screening, and assays for therapeutic efficacy.

The pharmaceutical industry has come a long way from the origins of drug discovery and development, which dates back to the early days of human civilization. Key discoveries of the 1920s and 1930s, such as insulin and penicillin, were mass-manufactured and distributed broadly. The industry picked up in earnest from the 1950s as a result of the development of systematic scientific approaches, an advanced understanding of human biology (including DNA), and sophisticated manufacturing techniques.

The idea that the effect of drugs on the human body is mediated by specific interactions of a drug molecule with biological macromolecules (in most cases proteins or nucleic acids), led scientists to the conclusion that individual chemicals are required for the biological activity of the drug. This made for the beginning of the modern era in pharmacology, as pure chemicals, instead of crude extracts, which are essentially mixtures, became the standard drugs.

Numerous new drugs were developed during the 1950s and mass-produced and marketed through the 1960s, including Valium (diazepam) one the most prescribed drugs in history. Cancer drugs were a feature of the 1970s, followed in the 1980s by drugs for heart disease and AIDS.

Today pharmaceutical manufacturing is a concentrated industry, with a few large companies leading global production. It has been suggested that the research and development cost of each new molecular entity, or drug, is approximately $1.8 billion. The high cost associated with drug discovery and the ongoing need for new medicines have driven the development of cutting edge analytical equipment.

Analytical Instruments

The departure point for drug discovery is identifying a useful new drug candidate molecule from among millions of different molecules. To do this researchers need sensitive, fast, and stable analytical equipment.

"The pharmaceutical industry is one of the fastest growing industries and a significant portion of its sales revenue is reinvested into research and development of new products—an area that requires a wide variety of specialty gases and equipment," says Katrin Åkerlindh, Global Product Manager for Specialty Gases & Specialty Equipment at Linde Gas (*linde-gas.com*). "Both the pharmaceutical and biotech industries are heavily dependent on gases and chemicals, from high purity gases for laboratory use, to process gases for production processes such as chemical synthesis, sterilization gases, and gas mixtures to grow biological cultures.

"Linde Gas has been very successful in developing and providing solutions to meet the evolving needs of the pharmaceutical industry in terms of impact, commercial manufacture, good manufacturing practice controls, scale-up issues, and process validation. Maintaining the integrity of the gas from the product source to point of use is one of the biggest challenges. Therefore, it is essential that the gas supply system be designed and built with the goal of excluding impurities and ensuring traceability through the supply chain."

Research and development take place in pharmaceutical laboratories using analytical instruments such as gas chromatographs with multiple detectors, liquid chromatographs coupled with mass spectrometers, ultraviolet/visible (UV/VIS) spectrometers and nuclear magnetic resonance (NMR) spectrometers. These significantly accelerate research and development cycles, ultimately bringing beneficial drugs onto the market faster than ever before. Åkerlindh says the effective operation of these instruments depends on the use of the appropriate gases or gas mixtures.

One of the key items of analytical equipment harnessed to test these chemical compounds is liquid chromatography-mass spectrometry (LC-MS). LC-MS defines and detects the structure of the molecular compound first by separating the compounds in the liquid phase chromatograph and then by detecting them in the mass spectrometer. Specialty gas grades of nitrogen are used in LC-MS as a curtain gas. LC-MS units equipped with electrospray ionization use nitrogen for nebulizing, drying, and also as a curtain gas.

NMR spectroscopy is able to generate a 3D image or visualization of the compounds in solution, which allows the structure of molecules to be defined right down to atomic level. This allows researchers to develop a good understanding of the molecule and its function in the human body. NMR spectroscopy involves placing a sample in a strong homogeneous magnetic field and irradiating it with radio waves of defined frequency.

X-ray crystallography, one of the most powerful tools available to researchers for visualizing candidate molecules, is a method of determining the arrangement of atoms within a substance, in which a beam of X-rays strikes a molecular or atomic structure and causes the beam of light to spread into many specific directions.

"This information is very important in drug design," says Åkerlindh. "By understanding how bioactive molecules interact with a target protein or nucleic acid it is, in principle, possible to design ligands with improved affinity and specificity that may make useful drug leads. In addition to this structure-based approach to drug design, NMR is also useful as a screening tool in drug discovery programs to identify ligands that bind to target macromolecules."

NMR spectroscopy is built on very strong magnetic fields and magnets, which need to be cooled down to an extremely low temperature, and the liquid helium supplied to achieve this is used at a temperature of -269° Celsius. This temperature is so low that the liquid helium dewar is normally surrounded by a liquid nitrogen dewar at -196° Celsius to minimize helium boil off.

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"It's fascinating that the same molecule with the same chemical formula and composition can exist in mirror images of itself," comments Linde's Steve Harrison, Global Head of Specialty Gases & Specialty Equipment. "When broken down into its constituent atoms, the basic structure is exactly the same. So although the chemical formula of the molecule might be the same, the molecule can exist in different shapes, referred to as 'chiral variations'. While chiral molecules are mirror images of each other and have the same chemical composition, one of these mirror images might have no effect on a human body at all—or a damaging effect—while the other chiral molecule occurring in a different shape could be a 'wonder drug'. Visualization techniques such as NMR or X-ray crystallography move us one gigantic step beyond chemical analysis."

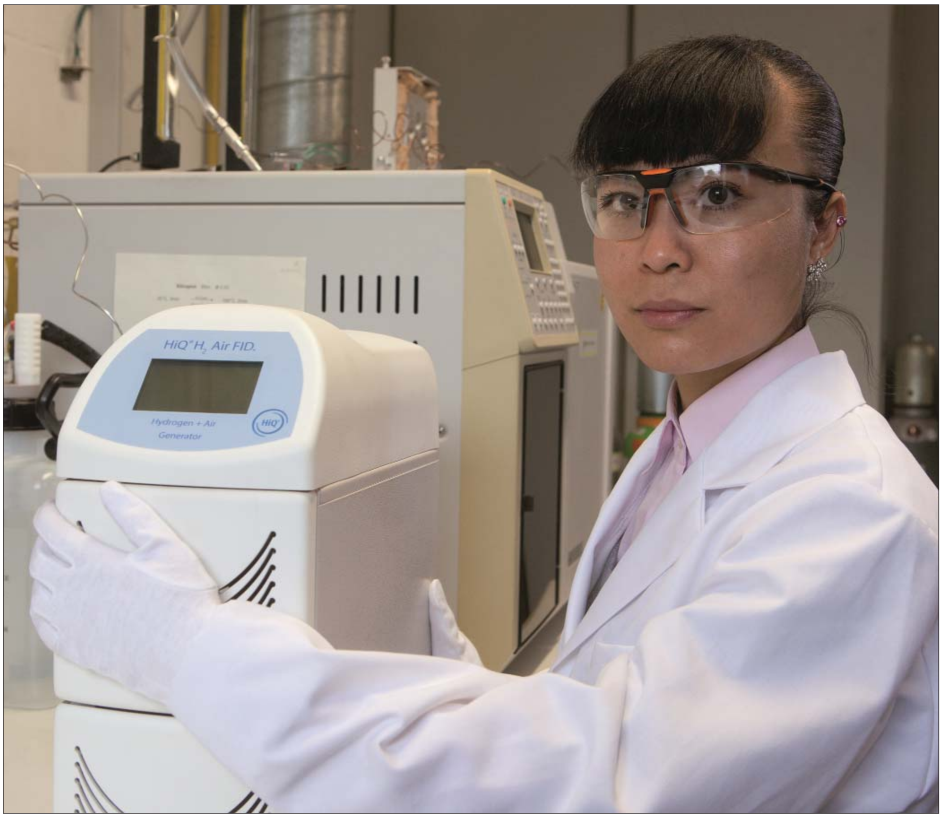
Supercritical fluid chromatography (SFC), available since the early 1980s, is a relatively recent chromatographic technique. What differentiates SFC from other chromatographic techniques is the use of a supercritical fluid as the mobile phase. SFC is used for the analysis and purification of low to moderate molecular weight, thermally unstable molecules. It can also be used for the separation of chiral compounds. Principles are similar to those of high performance liquid chromatography (HPLC), however SFC typically utilizes high purity carbon dioxide as the mobile phase.

It is interesting to note that the potential breakthrough antibiotic candidate Platensimycin, initially found in soil microbes, was identified and developed using a combination of HPLC, two-dimensional NMR and X-ray crystallography. And the latest generation of anti-cancer drugs has been possible through the use of modern sophisticated analytical techniques.

Trusting the Result

"With the immense cost associated with bringing a new drug to market and the speed at which companies are required to do this today, finding the correct molecular candidate and then being able to trust in the validity of the result is absolutely essential," says Åkerlindh. "The purity level of the specialty gases involved in this process, as well as the integrity of gas from the product source to point of use, is therefore critical."

Linde Gas also supports the drug discovery industry with liquid cryogenic gases used to store molecular compounds and biological material, or biopharmaceutical drug candidates, which require extremely low temperatures. Nitrogen freezers are ideal for this type of storage, achieving temperatures down to -196° Celsius. Linde Group UK subsidiary, BOC, has recently begun to offer state-of-the-art cryogenic bio-storage facilities. Although BOC has been supplying liquid nitrogen to customers for the past 50 years, the establishment of proprietary cryobanks is a sign of a definitive shift in the pharmaceutical industry that is seeing business opting to focus on their core competencies and outsourcing other requirements to appropriate service providers.



Specialty gases supplied in cylinders are sometimes unsuitable, either for transportation or safety reasons, so onsite gas generators offer an alternative, allowing for complete control of gas production.

Drug Integrity

Amid the many breakthroughs and improvements constantly taking place in the drug arena, the problem of counterfeit drug production has arisen. "This makes it critical for authorities to test the pharmaceuticals on sale in their markets, randomly and periodically, to ensure they are not potentially harmful counterfeits," comments Harrison. Analytical techniques are critical to identifying and avoiding malpractice in the manufacture, sales, and distribution of drugs.

Harrison says that modern drug discovery could not take place without today's advanced analytical instruments and that these instruments could not operate effectively and reliably without high purity specialty gases. Gas quality can often affect the accuracy of these instruments and Linde offers its HiQ® line-up of pure gases, gas mixtures, and precision engineered gas supply systems to the drug discovery industry. Carrier gases and calibration mixtures with known degrees of accuracy, purity, and composition are an essential part of the HiQ specialty gases product program. Linde's traceable VERISEQ® pharmaceutical grade gases are suitable for manufacturing of pharmaceuticals and active pharmaceutical ingredients (APIs).

"Where there is a demand for gas products in such areas as production, growth of biological cultures, environmental mixtures, sterilization, or chemicals, we are able to offer the right product for each application," Harrison says. "In some cases, cylinder, or liquid gas supply might be unsuitable. This may be for safety reasons or due to difficulty in cylinder transportation. For these situations, Linde has a range of small and reliable gas generators which produce gas onsite, which allows for complete control of gas production. Another advantage is that there is no need to store large amounts of compressed or liquefied gas, since there is access to newly produced gas. Gas generators are small and allow for flexibility in laboratory set-up owing to their portability." The HiQ specialty gas generator program includes high purity no-maintenance hydrogen generators (up to 99.9999% purity), LC-MS nitrogen generators up to 99.999 percent purity, and Ultra Zero air generators. ■

For further information on Linde's products and services that support drug discovery, email press@linde-gas.com.