The importance of Raman spectroscopy as an analytical tool is based on the ability to probe the unique vibrational and rotational modes of molecules in various materials. These phonon interactions induce material-characteristic frequency-shifts (Stokes shifts) in the scattered light from the illumination laser. This fingerprint region is accessible with most commercial Raman instruments and provides valuable information about molecules such as aromatics, carbonates, sulphates, silicates, oxides and hydroxides within the 500 to 1500 cm\(^{-1}\) range, and hydrogen interactions with carbon, nitrogen and oxygen at around 3000 cm\(^{-1}\).

More recently, there is also a lot of interest in accessing the low-frequency Raman spectroscopy region (< 10 cm\(^{-1}\) to 200 cm\(^{-1}\)). Raman shifts in this frequency range give access to lattice vibrations of molecular crystals and have the potential to more directly probe intermolecular interactions in solid materials. The low-frequency Raman region probes the same low-energy vibrational and rotational modes of molecular structures as terahertz spectroscopy (300 GHz to 6 THz). This THz region of Raman spectra contains important structural information about the molecules or crystal lattices under investigation (Fig. 1). For example, being able to determine the structural form of the Active Pharmaceutical Ingredients (API) is a primary objective in the pharmaceutical industry during drug development, manufacturing and quality control. APIs exhibit polymorphism, which is characterized as having identical chemical compositions but different solid-state structures that may affect the bioavailability and therapeutic index, and in turn could lead to compromised efficiency of any final drug product [2 – 3]. Specifically, low-frequency Raman spectroscopy provides an avenue to probe polymorphic structures of pharmaceutical systems before and after tableting [1]. Probing the low frequency Raman region has several advantages over existing techniques such as ease of collecting data (compared to traditional methods like X-ray powder diffraction and differential scanning calorimetry), collecting spectra that contain a lot of structural information as well as being able to discriminate crystalline forms.

The low-frequency Raman region for measurements of lattice phonons in pharmaceuticals has become more accessible in recent years with advances in precise optical filters and narrow linewidth lasers that have the required frequency stability. Therefore, low-frequency region investigations in pharmaceutical products have made the transition from the academic laboratory with customized laboratory set-ups to pharmaceutical labs and production lines. By equipping Raman microscopes with...
Raman are similar to the notch filter characteristics; the laser line has to be narrow and provide a side-mode suppression ratio (SMSR) of at least 60 dB at less than 5 cm\(^{-1}\) from the main peak. The spectral linewidth of the laser limits the spectral resolution of the recorded Raman signal, i.e., how small a difference in Stokes shift can be detected. However, the spectral resolution of a Raman spectrometer does not only depend on the laser source. In addition, the groove density of the diffraction grating, the spectrometer focal length and, in some cases, the pixel size of the detector are important. For most fixed-grating systems, the laser linewidth should be a few tens of pm or less in order not to limit the spectral resolution of the system. Related to the linewidth parameter is the frequency stability or spectral stability of the laser. The laser line must be fixed in wavelength while the spectrogram is being recorded in order to preserve the spectral resolution or to stay within the notch filter’s spectral range. Typically, the laser should not drift more than a few pm over time and over a temperature range of several degrees. In addition, the laser line has to provide sufficient output power at a suitable wavelength for the specific material under investigation.

**Narrow-line diode lasers**

Laser sources suitable for Raman spectroscopy at 785 nm which for many Raman applications is the most ideal illumination wavelength, can be produced from AlGaAs-based semiconductor devices. Depending on the emitter size and geometry, they can be designed to emit single-transversal mode beams (lower power) or multi-transversal mode beams (higher power). Semiconductor lasers have a broad gain spectrum and therefore a lasing bandwidth of typically > 1 nm. Their long spectral tails stretch to several tens of nm from the main peak. They can be made to emit spectrally single-mode radiation by introducing distributed wavelength selective gratings (DBR/DFB) into the chip structure. DBR/DFB lasers at around 780 nm are available at up to a few tens of mW output power. As an alternative for higher power levels, it is possible to turn the broad-band emission from a semiconductor laser into narrow-band by building an external cavity with a separate wavelength-selective cavity element. In this way, the stimulated emission from the laser will be frequency-locked to the spectral distribution of the feed-back from the wavelength-selective element. A conventional way for the construction of such frequency-locked semiconductor lasers is to build an external cavity using a Volume Bragg Grating element (VBG) (Fig. 3).

The output beam from the 785 nm semiconductor emitter is collimated before reaching the VBG element, which reflects a fraction of the light with a narrow spectral distribution back into the semiconductor. A draw-back for both DFB/DBR and conventional VBG frequency-locked laser devices is that a fair amount of broad-band Amplified Spontaneous Emission (ASE) from the semiconductor is still emitted from the laser device. This limits the SMSR ratio to

[Image 2](fig2.jpg)  **Fig. 2** VBG filters are used for low frequency Raman due to the sharp cut-off needed to access the low frequency region.

[Image 3](fig3.jpg)  **Fig. 3** Typical laser design of a conventional wavelength locked diode laser with a partially transmissive VBG. In order to fulfil the requirements on spectral purity for low-frequency Raman, an additional clean-up filter is required to suppress the ASE (Fig 4a).
around 40 to 50 dB up to several nanometers away from the main peak. For these lasers to be useful for Raman spectroscopy, they have to be spectrally filtered with external clean-up filters. For low-frequency Raman spectroscopy, standard dichroic filters with a typical transmission bandwidth of 1 to 2 nm are not sufficient; instead, more narrow spectral filtering must be used, typically by adding a second external VBG element. This additional VBG filter makes the system more expensive and can be challenging to match spectrally to the specific output wavelength of the laser.

In order to overcome this drawback, we here present an alternative and patent-pending design for frequency-locking a semiconductor laser. Instead of using a partially transmissive VBG, a highly reflective VBG element is used as wavelength selective component in the external cavity. An intra-cavity polarizing element and a polarizing beam splitter control the level of feedback from the VBG to the emitter and the output coupling out of the cavity. In this way, only the stimulated emission is coupled out of the cavity and the broad-band non-stimulated emission leaks out of the VBG element. The resulting spectral purity is similar to what is achieved with an external VBG clean-up filter but with the use of only one single VBG element (Fig. 4).

To ensure the performance of such a laser, especially in guaranteeing the wavelength and frequency-locking stability, all optical elements are assembled on a single temperature-controlled platform using Cobalt’s proprietary HTCure™ technology with high-temperature cured adhesives to ensure robust and precise alignment of the cavity components as well as high level of thermo-mechanical stability and insensitivity to ambient conditions. In this way the wavelength stability and SMSR can be maintained throughout the life of the laser and in varying ambient temperature conditions.

### Outlook

Being able to access the low-frequency region in Raman spectroscopy promises better insight into the detailed composition of pharmaceutical drugs and also stronger Raman signal levels. By combining low-frequency Raman spectroscopy with microscopy techniques and multi-variate analysis it is possible to determine the crystallinity levels and distribution of polymorphic Active Pharmaceutical Ingredients (APIs) in a drug. This information is very important in pharmaceutical manufacturing to ensure the therapeutic quality of the final product. With the increased availability of precise narrow-bandwidth filters and stable narrow-linewidth laser sources with very high level of spectral purity, such as the 785 nm laser source presented here, the use of low-frequency Raman spectroscopy for investigation of pharmaceutical products is starting to transition from research laboratory settings to production-lines in pharmaceutical industries.

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