FUTURE ATMP MANUFACTURING PARADIGMS: LESSONS FROM HISTORY

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In the fifth part of this series of blogs, Dr David Seaward, 3P Founder and Projects Director, delves back more than 100 years into the history of the pharmaceutical industry to see what lessons might be learned for ATMP production.

PARALLELS FROM OTHER SECTORS: ORAL SOLID DOSE

Let's take a look at how the commercial production equipment for conventional therapies has evolved with time. For those of you familiar with TRIZ — the Russian acronym for Theory of Inventive Problem Solving — the development of technology within a sector tends to follow similar paths. On that basis, we can draw some parallels between how ATMP equipment and consumables are likely to progress based on what has happened in other pharmaceutical areas.

Until recently, the pharmaceutical sector has been dominated by so-called small molecules. These medicaments are traditionally swallowed and the catch-all terminology for them is oral solid dose or OSD.

The author well remembers being mildly chastised by a Pharmacy lecturer at Cardiff University for referring to a tablet as a "pill"! Pharmacists in Victorian times made their own medicines. They would mix active ingredients with excipients to form a paste that was rolled by hand using crude tools. The resulting "pill" was sold to the patient. This was superseded by compressing dry ingredients into tablets and placing pharmaceutical ingredients within a hard gelatine capsule.

A Victorian pill roller and a Brockedon metal pill die (now in the Science Museum)

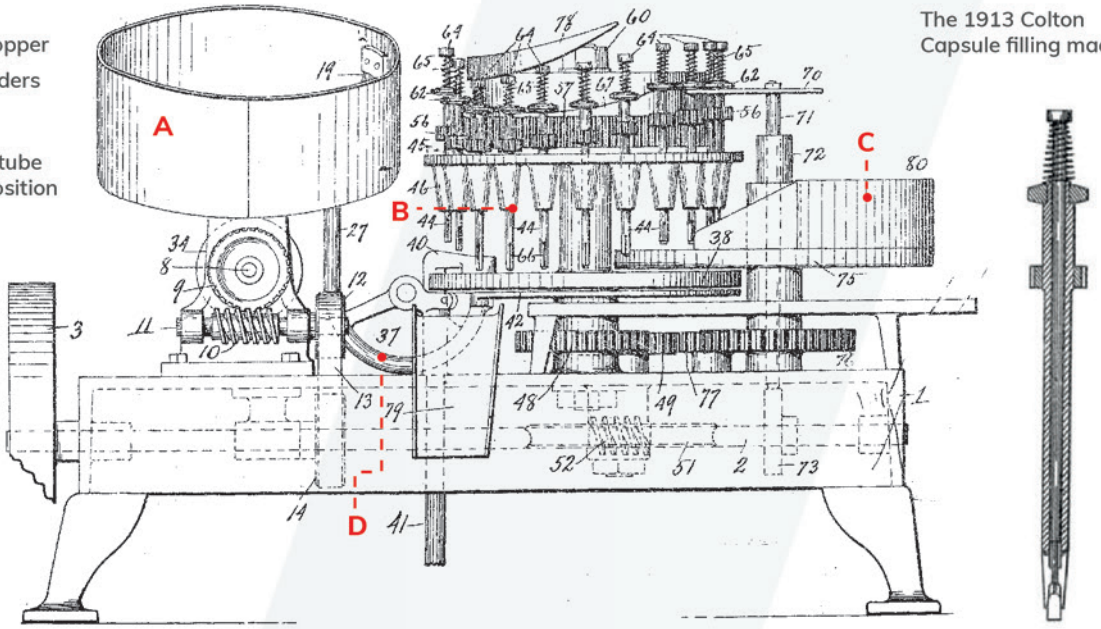
There was a sudden expansion in terms of the technology associated with swallowed therapies around the middle of the 19th century. This was driven by the need to provide a controlled amount to combat potentially dangerous overdosing with powerful new "potions" (such as digitalis to treat cardiac function in the form of dropsy, which is now known to be oedema, quinine extracted from cinchona bark to treat malaria [1820] and salicylates [aspirin] from willow bark).

In response to this trend and the need for tighter controls, the Pharmaceutical Society of Great Britain was formed in 1841. Around this time, both the two-piece capsule and the tablet appeared. In 1843, English inventor William Brockedon was granted a patent for a device capable of "shaping pills, lozenges and black lead by pressure in dies." Two-piece capsules can be traced to a few years later (October 1846) and Jules-César Lehuby, a Parisian pharmacist.

The first large-scale production of both occurred in the US. Hard gelatine capsules are attributed to the Detroit-based pharmacist, F. Hubel, who used standard gauged iron rods to serve as low-cost and accurate moulds on which to make capsules (capsule sizes still relate to the American gauge of steel rod originally used as the dip moulds).

In 1913, Arthur Colton patented an automatic capsule filling machine (below); the machine concept and dosator rods bear a striking resemblance to today's equipment, although dosators can be traced back to ancient Egyptian times when grass reeds were used to accurately dose early cosmetic powders. The process remains the same, although the materials of contraction have improved! 3P's latest precision dosator pin and tube sets use hardened stainless steel or tungsten carbide.

A - Empty capsule hopper
B - Capsule body holders
C - Powder hopper
D - Capsule transfer tube to rectification position

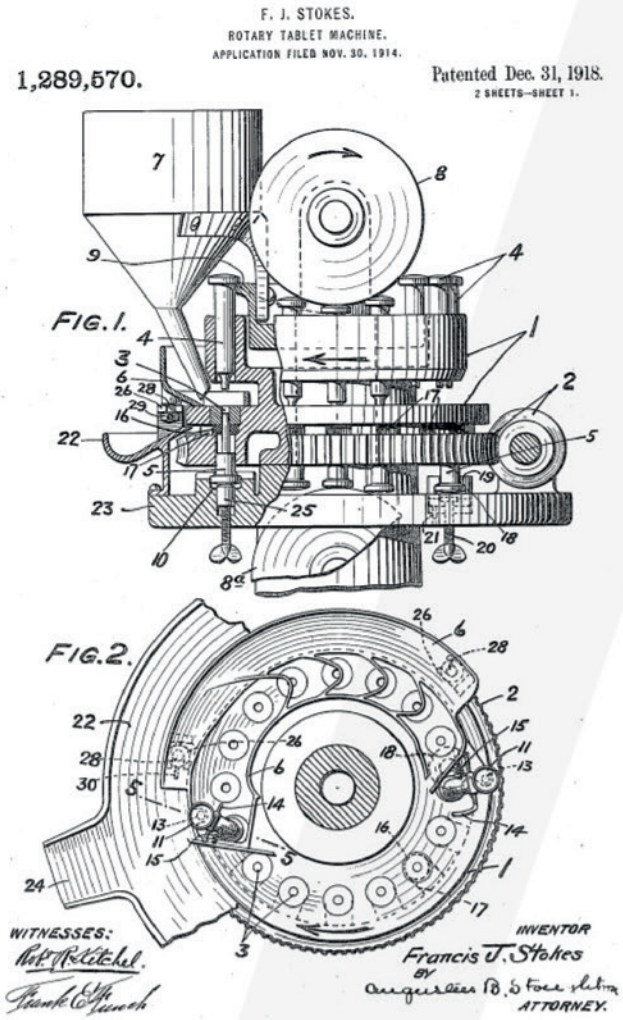


The 1913 Colton Capsule filling machine

Tableting began as a manual process whereby powder was introduced into the die and compressed by the upper and lower punches. This quickly led to cam-driven reciprocating machines that were capable of producing a thousand OSDs per hour. The first commercial rotary tablet press was manufactured early in the 20th century by Frank J. Stokes in the US. Stokes was initially making suppository machinery that, like tablet presses and tampon machines, use compression tooling as the primary unit operation. Stoke then turned his attention to tablet presses and moved to the UK to continue production.

His “B” and “D” type tool configuration is still used today. Upon his departure during World War II (WWII), his staff formed the Manesty company, which was eventually bought by Bosch in 2011 and was recently divested into the new Syntegon brand in 2020. Manesty retained the “B” and “D” configuration but “helpfully” changed the dimensions slightly. To this day, the industry still, unfortunately, has two types of B and D tooling; the American TSM standard and the European Euronorm version.

These two configurations are so similar that only a trained eye can distinguish them. Yet, they are different enough that they can’t be interchanged. Of course, there are other machinery companies that have long histories of supplying tablet presses. For example, Kilian (now part of the Romaco Group) can trace its history back to 1900 and German company, Fette, has produced more than 5000 presses since forming shortly after the WWII in 1948. Today, a modern Fette press can produce 1.6 million tablets per hour, possibly making it the fastest production machine on the planet still using the Stokes process.


F. J. STOKES.
ROTARY TABLET MACHINE.
APPLICATION FILED NOV. 30, 1914.

1,289,570. Patented Dec. 31, 1918.
2 SHEETS—SHEET 1.

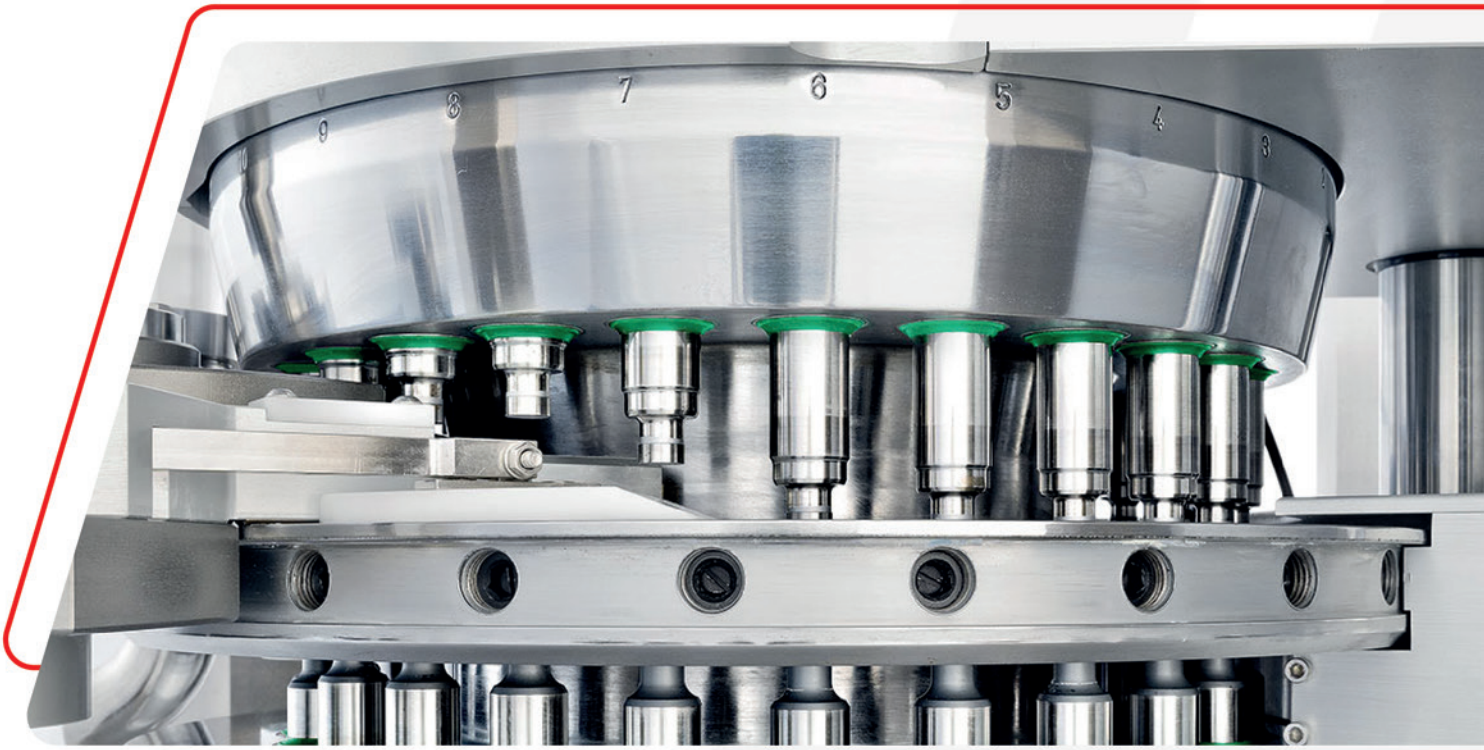
FIG. 1.

FIG. 2.

WITNESSES:
Robt. Ritchel.
Frank C. Ellis

INVENTOR
Francis J. Stokes
BY
Augustus B. Stoughton
ATTORNEY.

A Frank J. Stokes patent for a rotary tablet press (1914)



LESSONS (TO BE) LEARNT

An automation engineer thinks about the end effectors and the unit operations. Brockedon's manual press is, essentially, the same unit operation as the later reciprocating and rotary continuous motion tablet presses. The addition of sensors adds sophistication to a basic process that is fundamentally mechanical in nature.

Tracking the history of the tablet press, one can see that, despite company sales and mergers, the early developers of the technology are still around today. The original manual process patented by Brockedon was automated by Stokes. To make it faster, Stokes developed a rotary (continuous motion) rather than a reciprocating (intermittent motion) system. Brockedon's early invention can be traced to Stokes' patent, which can then be traced to Manesty and then on to Syntegon, etc.

Syntegon remain one of the leading suppliers of tablet presses as do the other early supplier Kilian. Fette are now the dominant supplier of tablet presses and are a relative newcomer being nearly 75 years old!

So how does this apply to ATMPs? If history is to repeat itself, the next 10 years will see significant activity regarding the automation of ATMPs. As will be discussed later, one size is unlikely to fit all! However, several core automation solutions tuned to specific therapies are likely to appear. The UK's cell and gene catapult categorises the capability of manufacturing sites as being either:

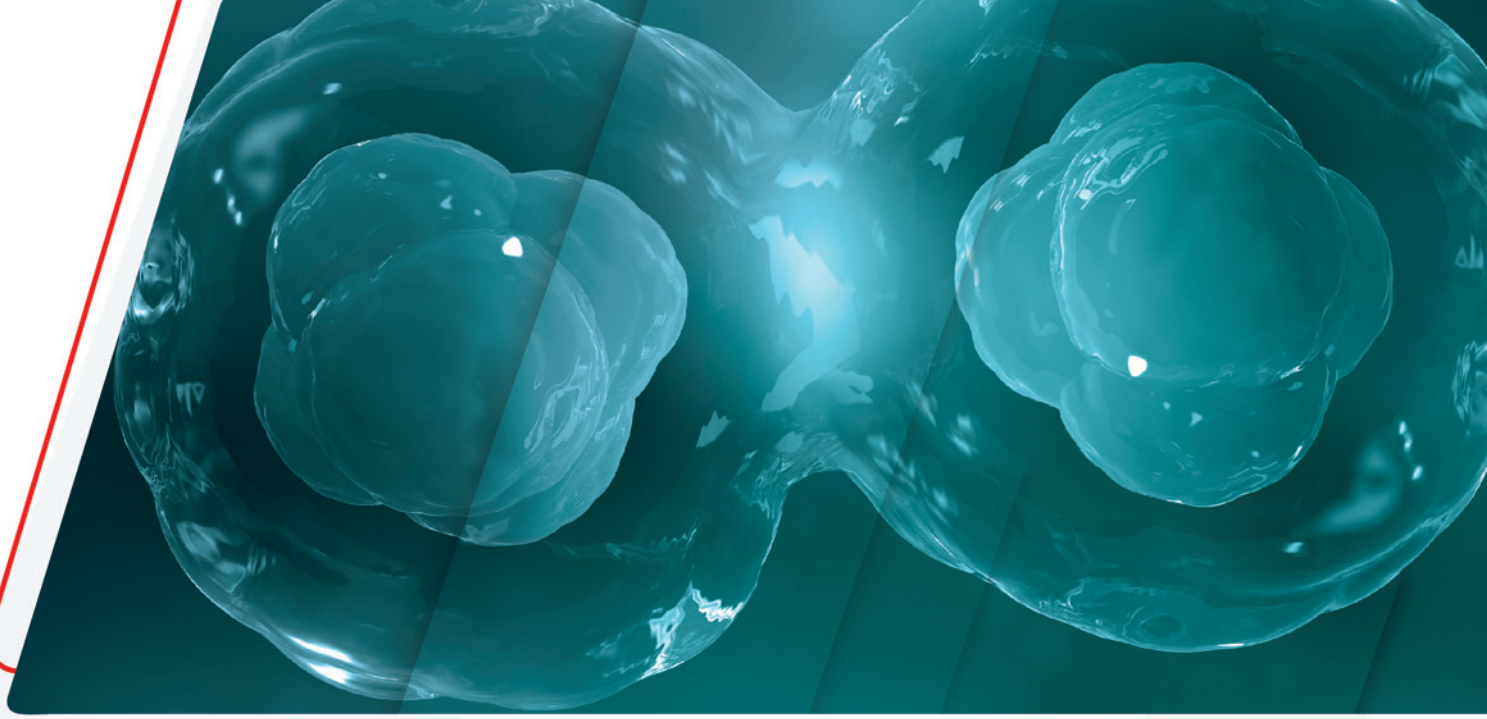
- 2D (adherent cell bioreactors)
- 3D (stirred bioreactors)
- Pluripotent stem cells
- Gene modification
- Immune cells
- Tissue-specific stem cells
- Autologous
- Allogeneic.

It will be recognised that the production of viral vectors in large stainless-steel vessels cannot utilise the same automation as, say, a CAR-T therapy or a stem cell (cord blood) one. It is likely that within each therapy type, two or three leading automation providers will emerge who will compete based on the quality/speed/cost of goods of the therapy their equipment produces. Within this mix will be the cost of the capital equipment and any "locked-in" consumables. Many are betting on selling an "ecosystem," whereby consumables are locked-in to the equipment (think inkjet printers and replacement cartridges). More competing companies will emerge to support this ecosystem around a lead core process in each sector. Vendors will appear to support upstream/downstream equipment and, probably, specialist consumables such as excipients and containers.

R1000 Robotic Capsule Filler

As discussed above, the OSD automation market took approximately 150 years to go from hand tooling to outputs of more than 20,000/min. This has driven down the cost of goods and improved the quality of the product. At the same time, innovation has reduced the time to bring a new OSD therapy to market (think GEA's continuous ConsiGma® technology or 3P's flexible R1000 Robotic Capsule Filler). This continued improvement stands on the shoulders of more and more detailed process understanding.

We are not, however, suggesting that ATMPs need to wait 150 years for great strides forward to occur in automation. As we all know, the rise of computing power allows engineers to significantly reduce the time it takes to develop novel technologies. Digital twins enable in-silico experimentation to shortcut real-world development. We now also have software programmes to fast-track CAD-based design, prototyping, DoE and analyse data to automate the gathering of process knowledge. Expect to see significant and rapid improvements being made in ATMP-related processes during the coming decade as investments are made to obtain process knowledge (think compression simulators used to understand the science of tablet formation).



A very recent trend is large venture capital investments in start-ups supporting the sector. The cost of goods is likely to halve every few years whilst product quality continually improves.

But, remember that Montgomery "Scotty" Scott, the fictional engineer from Star Trek, was correct when he said: "Ye cannae change the laws of physics." This remains as true for ATMPs as it does for other sectors. There will be process intensification initiatives to reduce the time it takes to produce a therapy; but, and it's a big but, these are natural processes that will have a natural limit. Cell lines will be selected for speed of division, we will learn more about macro and micronutrients and send just the right biosignal to ensure an optimum process for speed … but … there will be a natural limit that will drive other decisions and also influence the form of any associated automation.

This brings us nicely to the automation engineer's toolkit: "cycle" and "takt" times are very useful when forming a coherent automation strategy. As described earlier in part 4 of this series of blogs, an automation engineer typically breaks down a production system into a sequence of "unit operations." The duration of a unit operation is the "cycle" time, whereas the required time to meet a production target is the "takt" time.

There is usually a mismatch between different unit operations. Unfortunately, the cycle time for certain unit operations is often frustratingly longer than the takt time. Consider trying to make 1000 products during a 24-hour day involving two series processes — one that takes about 2 minutes and one that takes approximately 5 minutes: the takt time is actually 86 s or ~1.5 minutes and this is at 100% efficiency.

Straight away, the automation engineer is thinking in terms of two systems for the first unit operation, each of which is coupled to three for the second unit operation. The automation engineer earns their salary by finding ways to match the cycle times across all unit operations to the takt time (despite the laws of physics). For intermittent processes, it becomes necessary to multiply the number of stations performing operations.

The world's highest speed machines are continuous motion rotary machines, which can produce from thousands to tens of thousands of items per minute: these use multiple identical stations that incorporate multiple systems to match takt and cycle times. They also avoid cycle time losses owing to non-value-added indexes.

As the author has observed in multiple industries, most processes tend to start on the benchtop in manual mode and then progress to indexing/intermittent/batch processes. When much higher throughput is required, these same procedures become continuous. Choosing when to split them, and when to add buffers (storage), becomes critical.

One advantage of splitting is that stopping an upstream process doesn't necessarily stop the downstream one and vice versa. Essentially, an infinite buffer exists between unit operations. As systems become more reliable and robust, it becomes easier to bring processes together (sometimes with a small buffer).

If we use the tablet analogy, granulation traditionally occurs independently from tableting as a batch process. This is less cost-effective than the Holy Grail of a truly continuous process, during which powders are fed into one end of a system and coated tablets come out the other.

3P engineers assisted with the development of GEA's first ConsiGma® continuous granulator. This relatively recent innovation links a continuous (not batch) granulation system to a tablet press. The inherent flexibility provides a significant reduction in cost of goods for tabletting and expedites time-to-market for new pharmaceuticals. As the author experienced first-hand, much of the DoE work to understand the process became trivial compared with the impractical nature of repeating this with batch equipment: each experiment requires a long period of time and a significant amount of raw materials, which are often scarce and costly.

For a continuous process, the pilot and the commercial line are one and the same, meaning that scale-up challenges can be ignored. One of the challenges with ATMPs is that the unit operations involved may have cycle times that vary by orders of magnitudes. Cell expansion, in particular, is a relatively slow and yet simple process. Cells need to be kept at their optimum temperature and nutrient levels within an incubator for days. Upstream and downstream unit operations have cycle times of minutes and hours. Clearly, there is a disconnect driven by the "physics" of the system.

This would normally be addressed by having many pieces of equipment associated with the slow unit operations and few with the faster ones. This keeps the capital expenditure down by working all the equipment hard whilst minimising the physical space required (important when one thinks about the cost of cleanrooms).

IN SUMMARY

This fifth blog in the series has delved back more than one hundred years into the history of the pharmaceutical sector to look at what lessons might be learned for ATMP production. Despite mergers and takeovers, many originator companies are still in existence today, which is good news for current ATMP equipment innovators! Technologies have become increasingly refined whereas the core processes remain very familiar to those on century old equipment. It is likely that core ATMP processes will remain similar to those used today, but will be refined to increase both throughput and quality. Equipment complexity in terms of sensing and control will certainly increase.

The concepts of takt and cycle times were introduced in this blog. This is particularly important for ATMPs wherein the cycle times for different unit operations vary significantly. Although 3P engineers have some thoughts regarding how this might develop, there is as yet no clear lead solution to this conundrum. We suspect that each therapy area will develop its own preferred automation equipment and infrastructure. The needs of an autologous cell therapy are simply too different to, say, a viral vector-based gene therapy. What is very clear, though, is that there are some exciting years ahead.