A history of DPI capsule filling

How early DPI manufacturers overcame dosing and check-weighing challenges posed by filling capsules that weighed more than the inhalation formulation dosage

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In the 1960s, when Fisons Pharmaceutical Division introduced the Spinhaler device, the first DPI to use a hard gelatin capsule as a single dose container, filling the capsules initially presented significant challenges [1]. The Intal Spinhaler formulation contained equal parts sodium cromolyn (SC) (sodium cromoglicate BP), used for the prophylactic treatment of asthma [2], and lactose. Automatic capsule filling machines of the time were designed to fill relatively large quantities of powder for oral dosing, about 200-300 mg for a size 2 capsule that weighed 64 mg, but the Spinhaler dosage required only a 40 mg fill. In addition, the powder formulations often flowed poorly, and consequently, the machines had difficulty achieving consistent dosing.

Uniform dosing of powders into capsules relies on the formulations having good flow properties because all filling machines use volumetric dosing. The Fisons formulation used micronized SC since micronizing was the only method available at the time to achieve the aerodynamic diameters less than 5 μm necessary for delivery of particles to the lung [3]. Because micronized particles have high surface energies, they tend to aggregate, resulting in poor flow properties, and the micronized SC was no exception. Fisons added lactose to the formulation in order to improve the handling characteristics and found that adding lactose particles in the size range 70-100 μm produced the best emptying rates out of the capsules [4].

Two types of filling machines were available in the 1960s. The dependent type used the capsule body as a fixed volume measure, and the independent type used a separate dosator system to provide variable volume measurement [5]. Neither could deliver small doses accurately enough for this application. To obtain the low fill weights needed for their Intal Spincaps, Fisons modified a Tevopharm Cap III semi-automatic filling machine used for small-scale manufacture with an additional volume dosing plate that pre-measured 40 mg doses of powder prior to transfer into the capsule bodies.

Fisons required dozens of these machines, each of which required an operator, to produce a sufficient number of capsules for production. After the successful launch of the Spinhaler, demand for the product grew, and Fisons soon realized that it would need to upgrade from semi-automatic to fully automatic capsule filling machines in order to keep up. Realizing that they needed a better understanding of the powder properties of inhalation formulations before designing new dosing parts, Fisons enlisted the aid of researchers at Nottingham University to study the fundamental properties of lactose powders in dosator systems as used on machines manufactured by Italian company MG2 [6-9].

Achieving uniform filling with a dosing tube requires the formation of a powder arch at the open end so that no material drops out when the dosator moves from the powder hopper to transfer its contents into the capsule body. Studies performed by the researchers showed that the nature of the metal surface, the powder bulk density, the angles of powder/wall friction, and internal friction all factored into the arch formation [6, 7]. The knowledge gained in these studies led to the construction of an instrumented MG2 capsule filling machine simulator [8]. In order to solve the problem of attaching electrical leads to gauges on the moving dosator of the standard MG2, the simulator consisted of a stationary machine filling turret fitted with a single dosator around which the powder hopper revolved.

After validation, the machine demonstrated that it could satisfactorily fill fine cohesive powders over a wider range of compression settings than coarse, free-flowing powders [9]. The dosator nozzle produced the best results using the minimal amount of compression necessary for powder retention. Fisons eventually used MG2 machines fitted with mini-dosators to fill product successfully at the speeds required.

Fill weight checking systems

The typical powder fill weight for capsules taken orally measures about 4 to 5 times the capsule shell weight, so for all practical purposes the shell weight can be ignored. As a result, the standard method for controlling the filling of standard capsule products involves gross weight checking systems. Because the Intal Spinhaler capsule shell weighed approximately 150% more than the powder fill weight, that method was not viable, so Fisons initially checked fill weights by emptying the powder from a capsule per pharmacopeial methods.

In order to fully automate the system, Fisons developed a sampling station for the MG2 machine that collected the dosed powder directly into a container for weighing. Recent development in high speed weighing machines has further improved the ability to control powder dosing at low weights. The MG2 G100 computer-controlled pre-weight machine has a continuous fill weight adjustment system that weighs each capsule before and after filling to assure a 100% product check and operates at 90,000 capsules/hr at fill weights of ≥ 3 mg/capsule (Fig. 1).

Another company, Harro Höfliger, has developed a vacuum drum system that can dose capsules with weights < 1 mg, meeting a growing need due to the increase in potency of newer actives and formulations that do not use carrier particles. This new system employs a cylinder with sets of accurately drilled cavities in its surface. The cylinder forms the base of the powder hopper and as it revolves, the machine uses suction to fill the cavities with powder (Fig. 2). Compressed air then blows the pre-measured powder out into the capsule bodies. Blasts of air also clean the cavities before refilling. Harro Höfliger's modular machine, the Modu-C, offers an optional unit that weighs capsules pre- and post-filling (Fig. 3).

Figure 1

The MG2 G100 pre-weight capsule filler.

Photo courtesy of MG2

Figure 2

Harro Höfliger vacuum drum filler

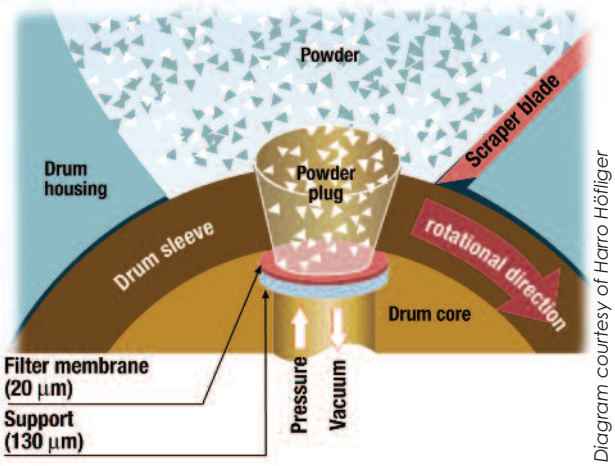

Diagram courtesy of Harro Höfliger

Figure 3

Harro Höfliger Modu-C capsule filler

Photo courtesy of Harro Höfliger

Recent trends

Over the years, the trend in DPI development has moved away from the original capsule-based devices to systems using reservoirs or individual blisters, and a wide range of device types are currently in development. Hard capsules, however, have evolved to meet the challenges of DPIs, especially with the development of hypromellose capsules that provide a low moisture content environment to aid product stability, with improved puncturing properties, stability over a wide range of conditions, and better microbiological profiles. DPIs based on capsules generally consist of relatively simple devices and, as such, provide platforms for the rapid development of new products, therefore helping to reduce the time to market, a critical feature in all development programs.

Recent trends in formulation have involved particle engineering to produce particles of specific size, density, morphology, and surface characteristics, achieved through techniques such as spray-drying, controlled crystallization, and supercritical fluid technology [10]. Developers have employed these techniques as a way to make powders that have better properties for effective administration and, in doing so, have improved handling characteristics that lead to faster and more accurate capsule filling as well.

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