

Manufacturing and Quality Control of Liquid-Filled Two-piece Hard Capsules



In the pharmaceutical market, hard capsules, together with tablets, are the most common dosage forms for oral administration. Concerning the manufacturing of solid dosage forms on an industrial scale, it is broadly recognised that powdered formulations are incorporated in two-piece hard gelatin capsules, while liquid or semi-solid formulations are incorporated in soft gelatin capsules, which are sealed during the filling process. However, sealing of two-piece hard gelatin capsules can be accomplished, thus allowing the incorporation of liquid or semi-solid formulation.

The use of two-piece hard capsules for the purpose of carrying liquid or semi-solid formulations appears to be an attractive strategy, but its potential has been poorly explored by the pharmaceutical industry. The current perspective presents a promising future for this “new” dosage form intended for the delivery of drugs or other substances which may be incorporated into a liquid or semi-solid matrix of lipophilic or hydrophilic nature.

The technology for obtaining two-piece hard capsules filled with a liquid or semi-solid formulation is relatively simple. The production of the dosage form is carried out in appropriate facilities with specialised equipment, under suitable and controlled conditions of temperature and humidity. Basically, the manufacturing process includes multiple steps, namely content preparation, filling, sealing or banding of the filled two-piece hard capsules, followed by drying of the sealed/banded filled two-piece hard capsules. The process for the production of liquid-filled two-piece hard capsules is also simpler as compared with that used to obtain soft gelatin capsules and, regarding the filling of powders, the problems of weight variation are reduced, and cross-contamination is virtually eliminated.

The use of two-piece hard

capsules proves to be suitable for substances showing low melting point, hygroscopic and oxidation sensitivity, or those requiring an oral absorption optimisation. Today, the vast scientific literature presents that this dosage form, in addition to promoting an increase in bioavailability as compared to the tablets, constitutes a simple way to obtain different release profiles from a unit dosage.

Some products presented as liquid-filled hard capsules are already available worldwide, namely in Europe, USA, Middle East, Australia and Japan. Today, two major companies are investing in this dosage form by providing two-piece hard capsules, machinery and technical advice: Shionogi Qualicaps and Capsugel. Other midsize companies working in the development and manufacturing of finished products are LiqFillCaps (Portugal), Encap Drug Delivery (Scotland), RentschlerPharma (Germany), and Pharmaceuticals International, Inc. (United States).

The two-piece hard capsules intended to be filled with liquid or semi-solid formulation have the same composition as conventional hard capsules. Conventionally, the gelatin hard capsules are the first choice, although gelatin/polyethylene glycol (gelatin-PEG) and hypromellose (HPMC) hard capsules could be used depending on the nature of the material to be filled. In spite of the fact that the ordinary two-piece hard capsule could be filled with liquid or semi-solid formulation, it is preferable to have a specifically designed hard capsule for secure containment of liquids and semi-solids. This design is found in LiCaps™ developed by Capsugel. What could be derived from the extensive experience of LiqFillCaps™ in manufacturing this type of dosage form is that the ordinary two-piece hard capsules (gelatin or HPMC) are perfectly feasible when the filling material is liquid at room temperature and viscous enough to not leak from capsule before applying sealing or

banding, or liquid and viscous enough at elevated temperature but semi-solid at room temperature.

The preparation of the hard capsule content includes steps common to any manufacturing process, namely weighing of the formulation components, and the mixture of the components in a predefined sequence and under predefined conditions of temperature, pressure, and agitation. The mixture can be processed at room temperature (25°C) or higher, and on agitation or ultrasonication, depending on the characteristics of the formulation components and the desired type of lipidic system. In order to obtain a robust process, thermal and rheological characteristics of the filling mixture are to be considered. Generally, the viscosity of the filling material should be between 0.1 Pa·s and 25 Pa·s, thus filling can be achieved with accuracy and precision. However, the maximum viscosity is determined by the characteristics of the filling pumps of the filling equipment. Concurrently, the viscosity of the filling mass should allow a clear break from the dosing nozzle and the absence of stringing. The temperature of the filling mass should not exceed 70°C, a requirement particularly important in the case of semi-solid formulations. When the filling formulation consists of a dispersion, it is recommended that the particle size of the suspending active component should be smaller than 50 µm, however manufacturing practice confirms that a particle size smaller than 180 µm (the same as the size range required in the case of soft capsules) is perfectly feasible.

The process of two-piece hard capsule filling with liquids/semi-solids should employ suitable machinery. It is said that most capsule-filling equipment could be modified so as to enable filling of hot or cold liquids into two-piece hard capsules. The fact is that this argument is not entirely valid or feasible, but was true when in early times engineering adapted powder-filling machines for the purpose of

MANUFACTURING

liquid-filling. Nowadays, appropriate machines are available for the filling of liquids or semi-solids into two-piece hard capsules.

With respect to the lipidic composition of the filling material for two-piece hard capsules, it is observed that formulations are susceptible to oxidation to a greater or lesser degree. The process of filling the liquid material into the body of the hard capsule is very fast, especially when using a machine that could work at a high liquid-filling rate (e.g., 80,000 capsules per hour), leading to a very short time exposure to the air. Nevertheless the air bubble at the head of the liquid-filled hard capsule (since only approximately 90% of the hard capsule total volume could be filled) could be detrimental to the stability quality of the formulation itself. Only recently, LiqFillCaps developed and validated a system capable of ensuring a nitrogen-saturated environment at the liquid container and, most important, at the liquid-filling station of the equipment. The system developed by LiqFillCaps was able to decrease oxygen in the head space of the liquid-filled hard capsule to values below 5% depending on the nitrogen purge. For that purpose, the oxygen and nitrogen levels were measured using a needle-type oxygen microsensor suited for measuring oxygen distribution profiles. This nitrogen purge system for the liquid-filling of hard caps was shown to be essential when a highly sensitive to oxidation oil was filled into two-piece hard gelatin capsules. Measurement of the oxidative parameters (peroxide value and p-anisidin value) for the filled oil, with and without the nitrogen purge system, was compared. Evidence showed that the oxidative parameters were kept low and constant throughout the stability study under ICH conditions when applying the nitrogen purge system.

The sealing process is another critical step in the manufacturing process. Sealing prevents the leakage of the content of the hard capsules. The processes of filling and sealing of hard capsules may occur in separate operation units or by a continuous process. Within the methods described for that purpose, the most used is

banding technology. According to this technology, the equipment performing banding is fed with liquid-filled hard capsules. The capsules are positioned and guided to pass over the sealing disk that rotates in a sealing solution, transferring the solution on to the capsules, thus coating the junction between the cap and body. The Hicapseal® is an example of a device developed by Shionogi Qualicaps for the technology described above. Right after banding, filled hard capsules are directed to a continuous-loop conveyor belt of a drying unit. The drying unit allows the freshly applied band to dry while keeping its integrity. This sealing process has the advantage of allowing a good seal and easy scale-up. With regard to the sealing solution, it has the composition of the two-piece hard capsule, i.e. if gelatin hard capsules are used then the sealing solution is a gelatin solution which is kept warm at controlled temperature during operation (attention must be paid to the viscosity of the solution during operation due to solvent evaporation). If HPMC hard capsules are used, then an HPMC solution is employed, in which case it is an ethanolic solution which is kept at room temperature during operation (the same attention must be paid concerning viscosity of the solution during operation due to solvent evaporation).

Another sealing technology is the one developed by Capsugel, designated as LEMSTM (Liquid Encapsulation by Micro Spray). This technology involves the application of a micro spray water-alcohol solution within the gap between body and cap of the capsule, which lowers the melting point of gelatin, promoting the junction between the two pieces. Each capsule is individually sprayed, and drying occurs smoothly in a revolving cylinder.

The quality control of the finished product has to be held in appropriate facilities and conditions and through approved procedures for the various tasks. Manufacturing of hard capsules containing liquids or semi-solids starts with quality control of raw materials, including the hard capsules. During the manufacturing process, it is also necessary to implement control systems for intermediates as well

as in-process control (IPC) being fully validated, since these are an integral part of quality assurance. Thus, after preparing the filling mixture it is necessary to perform the IPC by analysing and determining the following parameters: viscosity, pH and drug content. After filling of hard capsules follows the process of sealing and banding. At this stage, assessments are made of the visual appearance (optical clarity/turbidity, and presence of particulates), sealing, and weight uniformity of the capsules. A usual and practical method to assess sealing effectiveness is to visually inspect a sample of sealed capsules submitted to negative pressure on a bed of soft paper after a predefined period of time (the test is only positive if oily spots are observed on the soft paper). The moment before the primary packaging, packaging material should be properly checked for identification and printing. The semi-finished product (hard gelatin capsules containing liquid) should be subjected to a microbiological control and assay for the drug content. After the secondary packaging, it is important to verify the following aspects: the number of capsules per carton, batch no, expiry date, label, and print literature. The subsequent analysis of the finished product consists of the determination of parameters such as identification and determination of the active substance, disintegration test, and dissolution test.

Helton Santos

Head of the
Department of
Pharmaceutical
Development
at Labialfarma
S.A. Graduated



in Pharmaceutical Sciences at The Federal University of Bahia (Brazil). PhD degree in Pharmaceutical Technology (2005) at the University of Coimbra (Portugal). Joined Labialfarma in 2004 as a member of the Department of Pharmaceutical Development. Member of the Center for Pharmaceutical Studies, from the University of Coimbra.

Email: heltonsantos@labialfarma.com