# Liquid filling in Hard Gelatin Capsules - Preliminary steps

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## Introduction

For more than 20 years, the liquid or semi solid filling of Hard Gelatin Capsules have been routinely performed by the Pharmaceutical Industry. Among the various aspects of this technique, the selection of the excipients or fills to be used remains a key step of the development process. Preliminary steps to be followed to identify suitable formulations are recommended:

- Determination of the water exchange and control of visual aspect
- Control of brittleness potential
- Accelerated stability testing

## Determination of the water exchange and control of visual aspect

Gelatin behaves as a hydrophilic polymer and as such its water content may vary depending upon the storage conditions. Equilibrium moisture, sorption - desorption isotherms have been described by many authors. Depending on the previous moisture/drying history the water equilibrium may be described by the following hysteresis curve (Figure 1). As long as the gelatin water content remains in the range 11 to 16 %, no significant effect has to be expected on capsules brittleness potential.

Another aspect of the gelatin film which has to be considered is its water vapour exchange. As any film, the water vapour transfer can be determined for a gelatin film. Internal studies have demonstrated that above a film thickness of 70 µm this phenomenon is constant. Our understanding is that this phenomenon is mainly driven by water sorption/desorption mechanism at the film surfaces. The transfer of the water vapour within the film (above 70 µm thickness) is not a limiting factor (Figure 2).

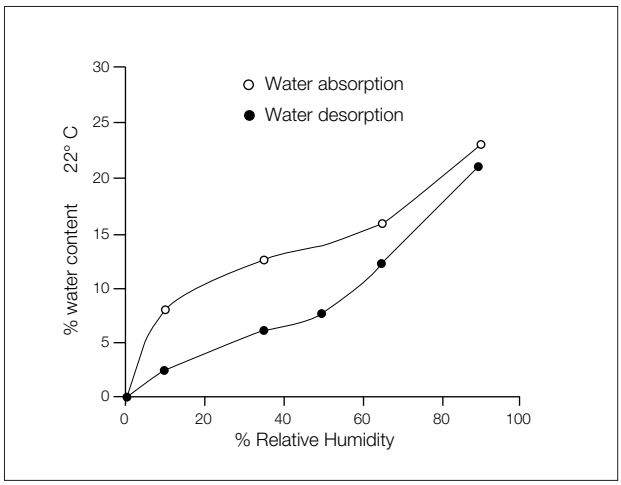


*Figure 1: Gelatin Sorption Isotherm*

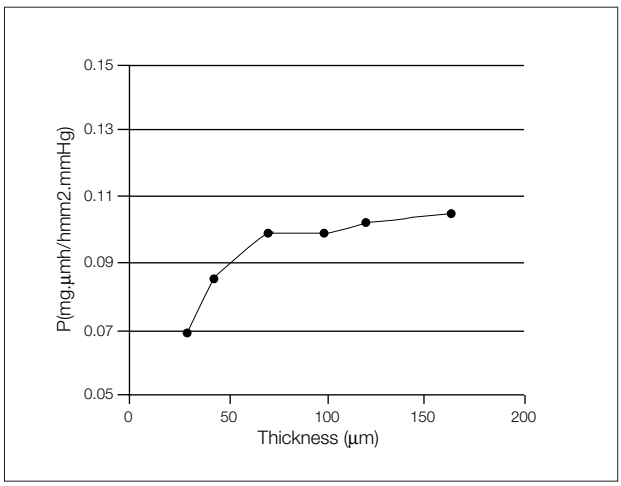


*Figure 2: Gelatin Water Vapour Transfer*

The importance of this water vapour transfer can be illustrated by the determination of the quantity of water absorbed by a hygroscopic dry powder (Carboxymethyl-Cellulose Sodium salt from Sigma chemical Co) filled into a Hard Gelatin Capsule stored at 50 % RH / room temperature (Figure 3).

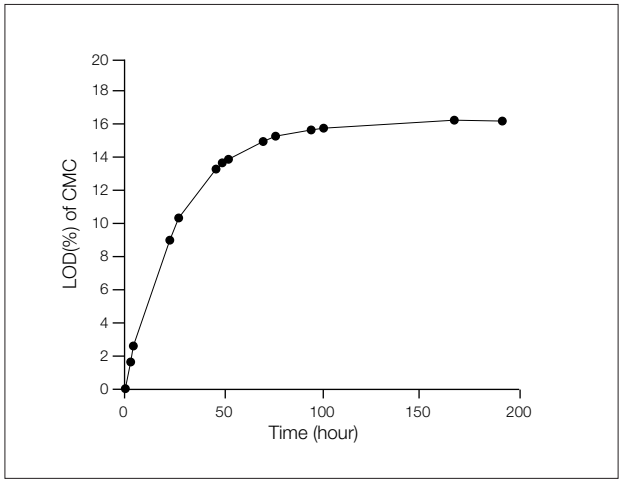


*Figure 3: Hard Gelatin Capsule Water Permeability*

More important for the liquid formulation into Hard Gelatin Capsules is the determination of the water exchanges as a function of the Relative Humidity of the ambient air. Screening tests have been defined to identify a potential hygroscopicity of the filled excipients by storage into dessicators at constant RH.

- 10 capsules are filled with the product to be tested
- These capsules are held in the upright position and stored in dessicators at various relative humidities: 2.5%, 10%, 30%, 50%, 65% RH
- After 1, 2 & 4 weeks the water content change is determined by weighing the capsules.

**Examples of products tested:**

A- Pharmaceutical formulation DH 1014/Bis Solid SMEDDS from Gattefossé.

| | % w/w |
|---|---|
| Gelucire 44/14 | 80 |
| Plurol Oleique | 10 |
| Lauroglycol FCC | 10 |

B- Lauroglycol FCC (Chemical denomination: Propylene glycol laurate. Supplier: Gattefossé) (Figure 4).

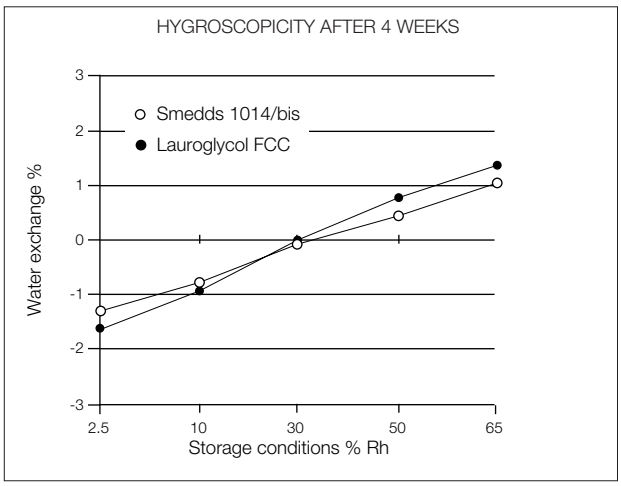


*Figure 4: Water exchanges of two Gattefossé products filled into Hard Gelatin Capsules*

As per comparison other excipients have been tested for their hygroscopicity into Hard Gelatin Capsules.

**Water exchanges in % w/w of excipients filled into Hard Gelatin capsules stored 4 weeks at constant Relative Humidity:**

| Excipient | 35%RH/RT | 60%RH/RT |
|---|---|---|
| PEG 300 | +4.6 | +14.7 |
| PEG 600 | +2.9 | +11.8 |
| PEG 4000 | 0 | +0.6 |
| Glycerin | +10.5 | +28.2 |
| Empty capsules | -0.4 | +1.9 |

**Example with Gelucire products from Gattefossé:**

| Excipient | 10%RH/RT | 65%RH/RT |
|---|---|---|
| Gelucire 39/01 | -0.8 | +0.5 |
| Gelucire 43/01 | -0.7 | +0.4 |
| Gelucire 44/14 | -1.0 | +0.8 |
| Gelucire 50/02 | -0.8 | +0.7 |

As a first indication we would define suitability of an excipient or a formulation for Hard Gelatin Capsule when water exchange is limited to -2% / +2% under above described test conditions.

In parallel to this step, we recommend to control the visual aspects of the Hard Gelatin Capsules (softening or leakers).

### Control of brittleness potential

A second key aspect of the gelatin capsule stability to be determined is the possible trend for brittleness. Few authors have published on this characteristic (1). Capsugel method is based on the determination of the resistance to impact of the empty shells (measured with a modified Mouton pendulum - Figure 5). This technique gives an accurate information by testing a limited number of samples (N=10).

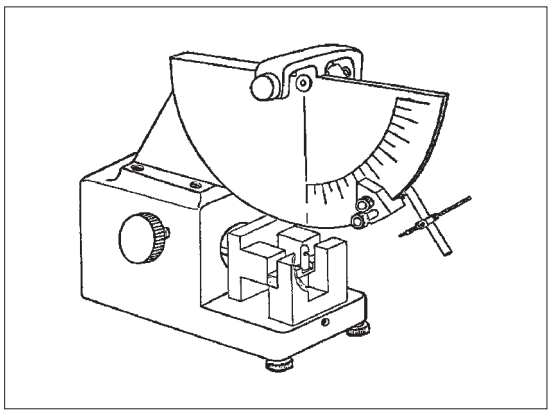

*Figure 5: Equipment for control of Capsule's Resistance to Impact*

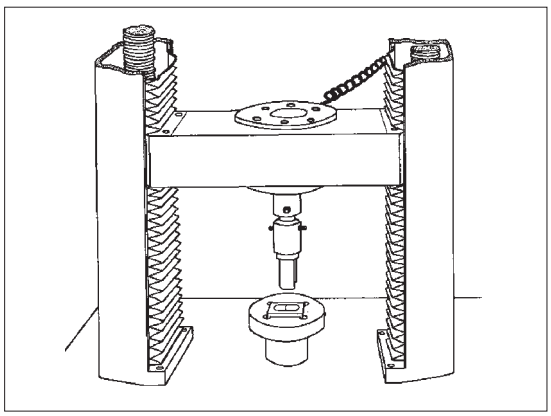

*Figure 6: Test set up for capsule's deformation test*

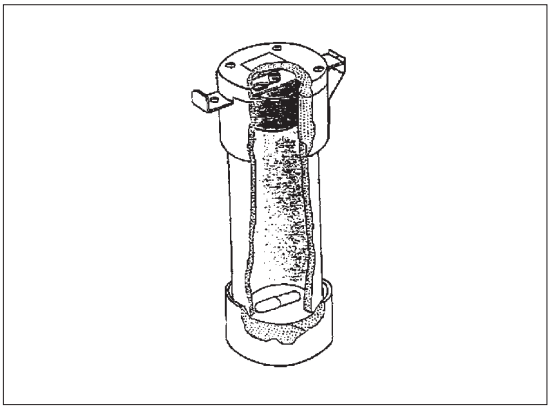

*Figure 7: Schematic view of a modified tube tester*

**Example of resistance to impact of capsules (stored filled with various Gattefossé products) tested on individual body or cap parts:**

| | Loss on drying (%) | Resistance to impact (mJ/mm) |
|---|---|---|
| SMEDDS 1014/Bis | 12.2 | 27 |
| Lauroglycol FCC | 12.4 | 25 |
| Acceptable range | 12-15 | >22 |

Other methods have been described (2, 3) to determine the potential brittleness of the capsules such as resistance to deformation of the filled capsules (Figure 6) or the tube test (Figure 7).

### Accelerated stability testing

A further step is the determination of the behaviour of capsules stored under accelerated stability conditions. From the various conditions recommended by the ICH3 (4), we have selected as first condition to be tested the storage at 40°C/ 75% RH.

We have selected the HDPE bottle as container and checked the Hard Gelatin Capsules dissolution stability after 1, 2, 3 and 6 months. Dissolution measurements are performed on emptied capsules refilled with Acetaminophen (USP method).

We have studied the dissolution behaviour of gelatine capsules filled with lactose powder exposed to formaldehyde vapour (5). This technique did enable us and other authors to better understand the importance of this mechanism (6). Capsules with

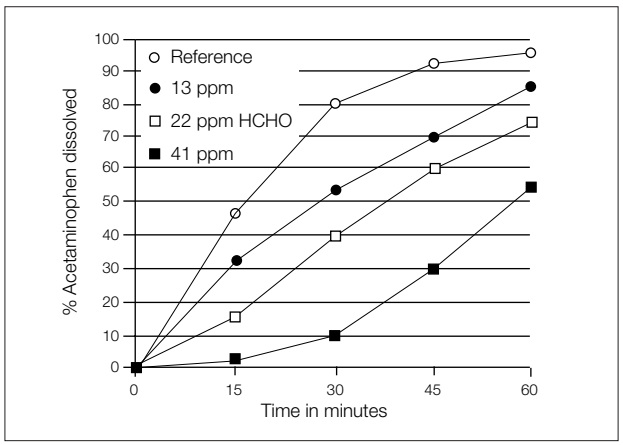


*Figure 8: Dissolution of Acetaminophen from capsules stressed with various levels of formaldehyde and stored at 50°C for 4 weeks*

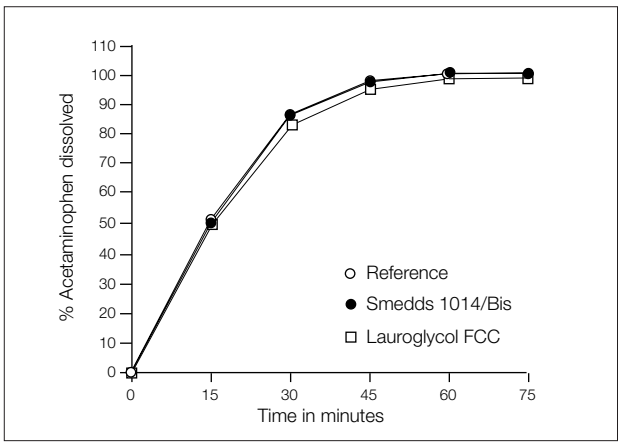


*Figure 9: Dissolution of Acetaminophen from capsules stored at 40°C/75%RH with various fills*

delayed dissolution in water could easily be prepared in our laboratory and tested with Acetaminophen (Figure 8).

Using the same approach, we have filled our gelatine capsules with various products selected from the range of excipients from Gattefossé and stored the filled capsules at 40°C / 75 % RH. After the defined period (1,2,3 & 6 months) the capsules are emptied from their fill and refilled with Acetaminophen to perform the dissolution test described. Results below (Figure 9), show that there is no interaction between the SMEDDS 1014/Bis or the Lauroglycol FCC and the gelatine capsules.

## Conclusion

The results obtained with the selected tests are summarized below.

With the three steps described above, preliminary selection of the appropriate excipient formulation for liquid or semi-solid filling into Hard Gelatin Capsules, can be performed at an early development stage, in the laboratory, without involving high cost or sophisticated equipment.

| | Solid SMEDDS 1014/Bis | Lauroglycol FCC |
|---|---|---|
| Water loss / gain | Less than 2% | Less than 2% |
| Visual aspect | No change | No change |
| Brittleness | Within range | Within range |
| Accelerated stability 40°C/75% RH - Dissolution | No change | No change |

## References

1. Mark J. Kontny and Carol A. Mulsky, Intern. Journal of Pharmaceutics, 54 (1989), 79-85
2. D. Cadé, APGI Colloque Nov 1994, Chatenay - Malabry, France
3. T. Yamamoto and all, Pharm. Tech. Japan, Vol. 8, N°11, 1992
4. Eur. J. Pharm. Biopharm. 41 (3), 194-195, 1995
5. D. Cadé, N. Madit and E.T. Cole, AAPS Pharm. Research Vol. 11, No. 10, p. S 147
6. G.A. Digenis; T.B. Gold; V.P. Shah; Journal of Pharmaceutical Sciences, 83 (7), 915-921, 1994