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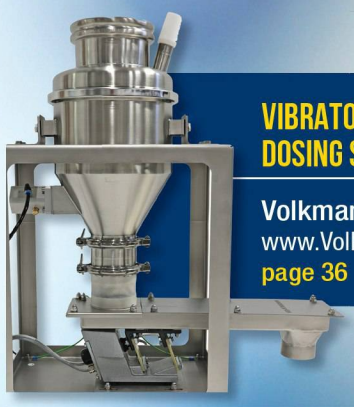

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THE PERFECT CLIMATE FOR CAPSULE STORAGE

By Martin Ginty, Munters

As a dosage form, capsules have been around for a long time. The first recorded patent for gelatine capsule production was in 1834. It would be reasonable to assume that after some 180 years of experience there would be no secrets about how to achieve optimal capsule quality and consistency. While that assumption is mostly true, things have also changed since the first capsules were produced. New technologies have entered the production space, formulations and ingredients have changed to meet market demands, and even the climate itself has changed with seasonal temperature and humidity reaching new levels. One thing that has already changed and will also continue to develop, is the need to produce capsules with consistent quality characteristics, particularly when producing GMP-compliant products. Not surprisingly, humidity control during the drying and storage processes plays a large role in achieving quality targets.

Capsule materials and characteristics

The most common material used for capsule production is gelatine. Regardless of the source and type of gelatine, the actual physical characteristics of different types of gelatine are similar from a drying and storage perspective. For example, the melting point of all types of gelatine is around 30°C to 32°C. This presents challenges for production in climates where temperatures regularly exceed this. As early as 1913, Eli Lilly first used air conditioning to allow production at times when the air temperature was above 30°C — prior to this innovation production stopped, as the gelatine would not set. Since then, some form of air treatment has become the norm in production areas.

After gelatine, hypromellose (HPMC) is also used to produce capsules. Its plant-based ingredients pose few dietary objections than animal-based gelatines, and it is well-suited to fillings that are sensitive to moisture or that may not work well with the residual moisture found in gelatine capsules (e.g. powders used in inhalers).

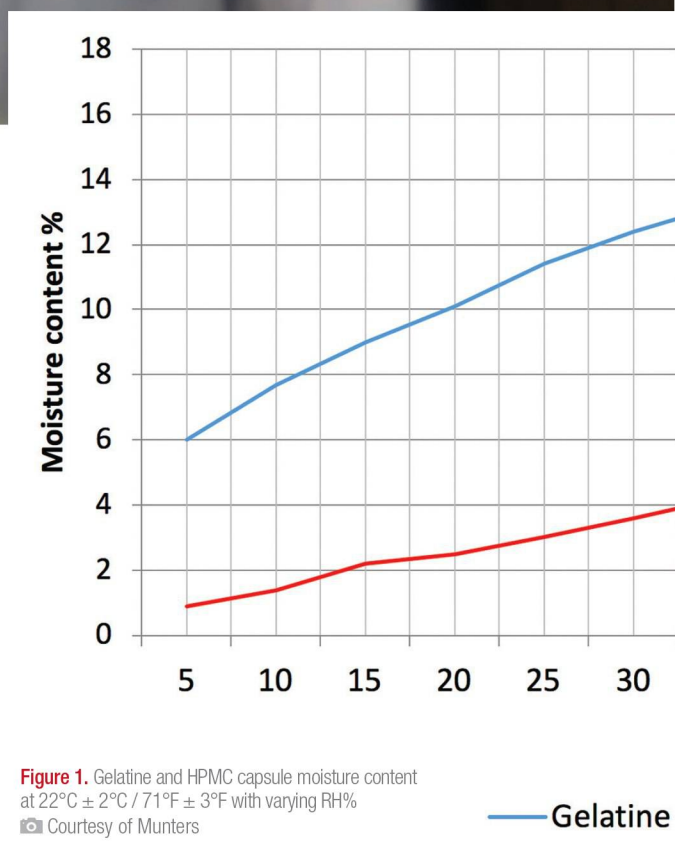

Figure 1. Gelatine and HPMC capsule moisture content at 22°C ± 2°C / 71°F ± 3°F with varying RH%
Courtesy of Munters

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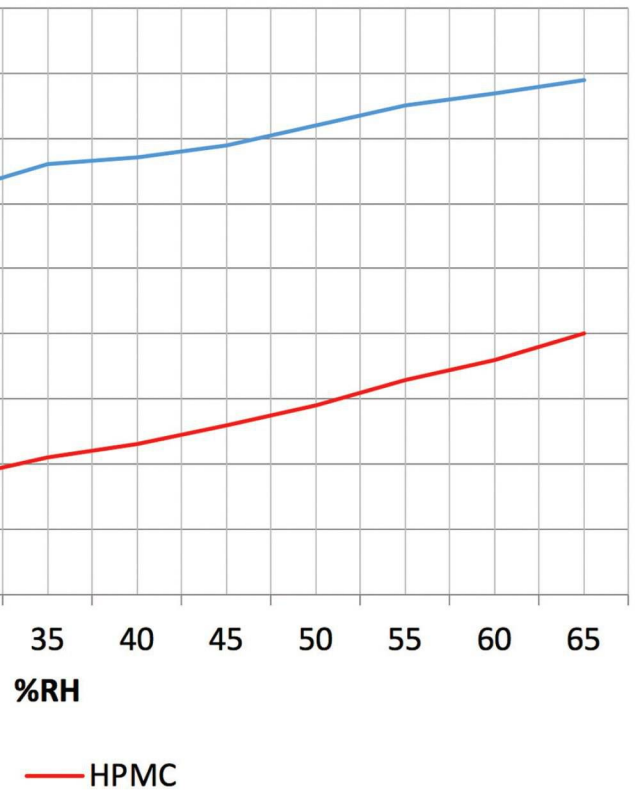
Gelatine type	RH%	Melting point °C
Lime processed ossein	25	31.5
	60	31
	85	>97
	95	86
50% Lime processed ossein, 50% Lime processed hide	10	33
	68	34.5
	85	>97
	96	86.5
Acid processed ossein	25	31
	60	31
	85	93
	95	53.5

Table 1. Effect of different RH% levels on dissolution temperature of gelatine films. Courtesy of Munters



Dosage Form	Storage conditions			Effect on dissolution	Visual observation
	Temp. °C	%RH	Time		
Hard gelatine capsules					
Chloramphenicol[a]	25	49, 66	32 weeks	No change in drug release	No apparent change in disintegration.
	25	80	32 weeks	No release till 1 hour	Gelatine shell failed to disintegrate.
	25	100	32 weeks	Significant decrease at 1 month	Gelatine shells were rubbery, soft, and difficult to handle.
Gemfibrozilb[b]	37	80	1, 2, and 3 months	Significant decrease at 1 month	Film formation after 1 month
Hydrophobic drug in various coloured capsules[c]	25	80	Ambient light, 2 weeks	Significant decrease	Swelled within minutes and formed a poorly disintegrating elastic matrix after 12–15 min. into the test.
	30	80	Fluorescent, 2 weeks	Significant decrease	The aged capsules swelled and formed a partially insoluble gelatine shell. A swollen, rubbery gelatine matrix, which enveloped the encapsulated powder, was noted during the dissolution.
	27	80	UV, 2 days	Significant decrease	Formed insoluble film.
Gemfibrozi (E)[d]	40	85	4, 8, 12 weeks	NA	Increase in disintegration time and evidence of gelatine cross-linking was prevalent.
Piroxicam (G)[d]	40	85	4, 8, 12 weeks	NA	Dramatic increase in disintegration time. Pellicle formation was observed in all tested capsules.
Development API with lactose-based granules[e]	40	75	12 weeks	Significant decrease	Noticeable pellicle formation (a palpable gel-like colourless film) inside capsules.
Org 12962[f]	40	75	1, 3, 4, 5, 6, 14 months	NA	Slower disintegration after 6 months.
Erlotinib[g]	40	75	4 weeks	Significant decrease	Not fully disintegrated at 15 min., with lump form covered by a gel-like film at 45 min.
Genentech development drug[h]	40	75	1 & 3 months	Significant decrease and variation	After 3 months, capsule disintegrated slowly. Some capsules appeared to be gelling with blend trapped inside, not ruptured until "infinity" at 250 rpm.

Table 2. Visual Observations on Gelatine Capsule Cross-linking Reported in the Literature. Courtesy of Munters

Moisture content of finished capsules

Empty gelatine capsules have a moisture content between 13% and 16% — they will become brittle if the moisture content falls below this limit, and will soften if it increases above it. Empty HPMC capsules have a moisture content of 3% to 6%. These capsules can be dried down to less than 1% moisture without losing their mechanical strength and becoming brittle. Regardless of the material used, this fluctuation can lead to some degree of compromised capsule strength and overall quality, so it needs to be considered from the very outset of production.

Moisture content of gelatine and HPMC capsules will vary depending on the ambient conditions as the moisture content will gradually reach equilibrium with the surrounding relative humidity level. Figure 1 shows the changes that occur after storage for one week at varying humidity levels.

Therefore, humidity must be considered when capsules are stored to ensure the required moisture content is maintained, particularly if water vapor exchange between the capsule and the filling may also contribute to the overall available moisture content.

Packaging and storage — how gelatine reacts to relative humidity

When capsules are packaged, attention should be given to the ambient conditions, as a small quantity of the surrounding air will be sealed in with the product. Depending on the volume of the packing container, this could introduce a quantity of water vapor that may affect the capsules. In general, HPMC capsules are not as vulnerable to this water vapor as gelatine capsules are, so from this point on only gelatine capsules will be considered.

Table 1 shows the effect on the melting point of gelatine films stored at various relative humidity levels after conditioning at 50°C for eight days. The melting point/dissolution temperature of the gelatine film was determined by placing the film in a water bath at 20°C, and the temperature was raised by 1.7°C per minute until the gelatine dissolved. It is interesting to note that the initial melting point of the samples was 32°C, which correlates to the gelatine samples that were stored in low humidity conditions.

At a relative humidity level of 85%, the maximum change in melting point is observed; excessive moisture absorption at higher levels increases the separation between gelatine molecules

and makes reformation of bonds more difficult. Increased melting point is a problem, as the gelatine will not dissolve as expected when the patient ingests the capsules.

High relative humidity causes by cross-linking

As shown in the data presented above, long-term storage of gelatine capsules at raised temperature and humidity levels (e.g. 40°C, 75% relative humidity for six months) changes the gelatine composition as cross-linking of gelatine molecules occurs. This reduces the solubility of the capsules — in the worst case, rendering capsules practically insoluble. Table 2 is a collection of observations from various manufacturers that show instances of gelatine cross-linking in actual products.

In addition to this, variations in relative humidity outside of the recommended levels can cause hydrothermal contraction in gelatine films. For example, a 0.6mm-thick gelatine film that is exposed to 80% relative humidity and 21°C reduces in size by 2.4% in relation to the overall film length1. Changes in the size of the capsules may lead to:

- Changes in the capsule dimensions and tolerances for closing
- Contents leaking
- Changes in physical appearance
- Decreased patient compliance if they feel the product is no longer stable

Correct storage and packaging are important to achieve maximum product shelf life and achieve target quality levels. As mentioned earlier, finished gelatine capsules have a 13% to 16% moisture content, so storing in the range of 35% to 65% relative humidity and 15 to 25°C (59 to 77°F) will maintain this.

By comparison, HPMC capsules contain less water than gelatine alternatives, and changes in moisture content has less effect on capsule dimensions.

In closing

Relative humidity can impact the quality of both gelatine and, to a lesser degree, HPMC capsules during production and storage. If the air is too dry, the gelatine capsules become brittle, particularly if they are kept in their unfilled, open state.

More seriously, the potential for gelatine to undergo cross-linking and hydrothermal contraction increases in relation to the relative humidity level, which leads to diminished product quality.

On the other hand, when the relative humidity level is too low, static electricity can build up in the production area. This leads to capsules sticking to each other or being difficult to package properly as the capsules are attracted to the plastics used on the production and packaging lines.

With accurate control of relative humidity levels, these problems can be avoided and product quality will benefit as a result. PR

References

- Figure 1: Capsugel Library - Performance Qualification of a New Hypromellose Capsule
- Table 1: Jopling, 1956 – Society of Chemical Industry
- Table 2: http://www.dissolutiontech.com/issues/201708/DT201708_A01.pdf
- [1]Calhoun and Leister, 1959

Martin Ginty is Global Pharmaceutical Industry Manager for Munters, a leader in energy efficient air treatment solutions based on expertise in humidity and climate control technologies. Ginty joined Munters in 2014 and is currently responsible for its overall product and solution offering for pharmaceutical applications worldwide. He has more than 20 years of experience in implementing national and international level automation and HVAC projects, and can be reached at Martin.Ginty@munters.de.

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