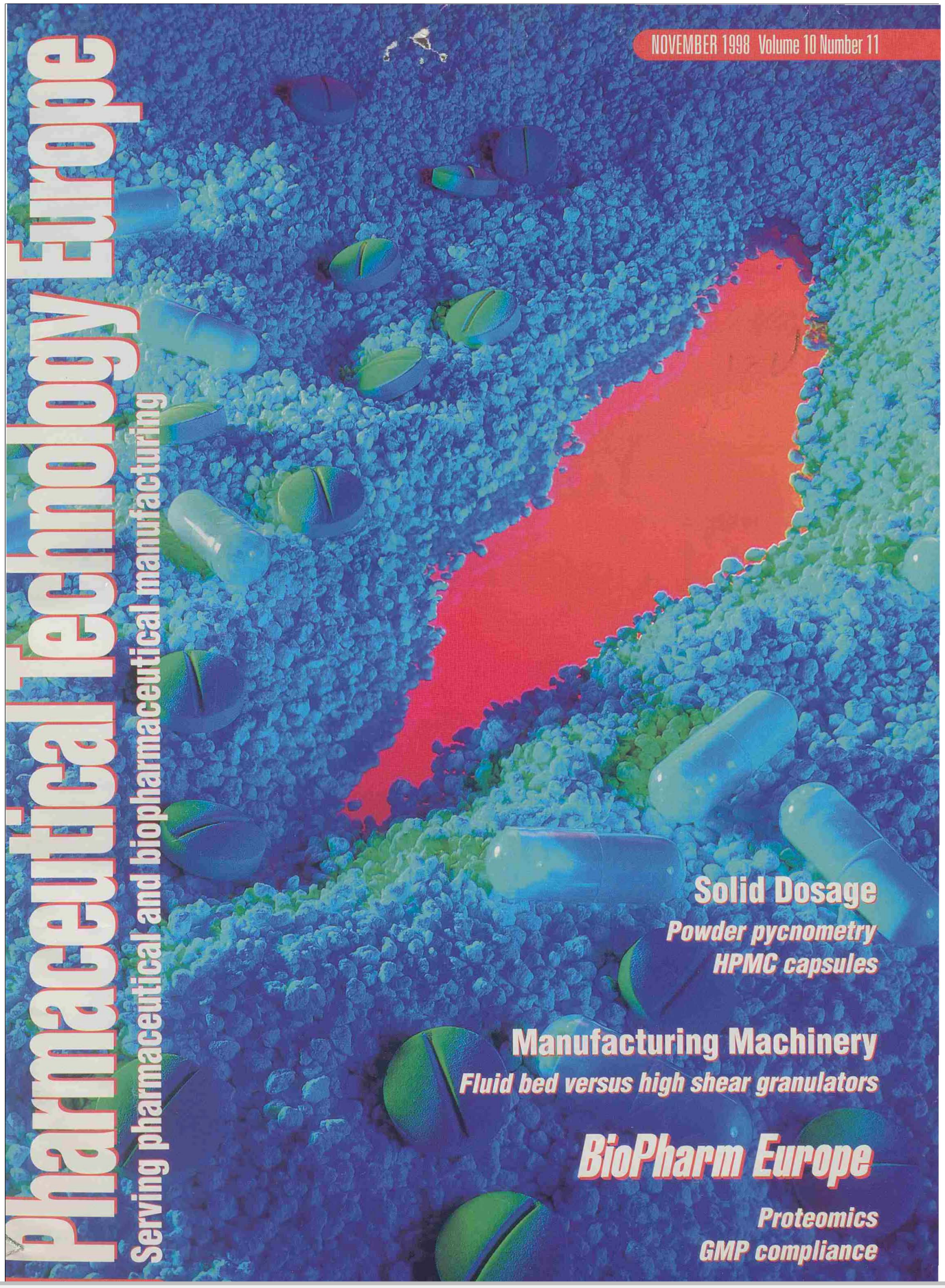

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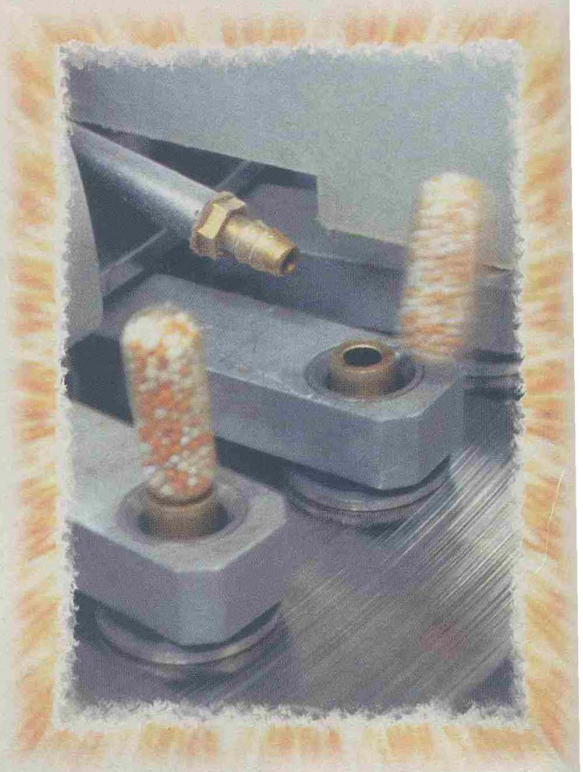
# HPMC Capsules — An Alternative to Gelatin



*Hydroxypropyl methylcellulose (HPMC) capsules are made of plant-derived materials and do not contain components of animal origin, eliminating problems with religious or vegetarian dietary restrictions. Unlike gelatin, HPMC does not have chemically reactive groups, dramatically decreasing the potential for reactions between the drug and the capsule shell. HPMC capsules have a naturally low moisture content, maintain mechanical integrity under extremely low-moisture conditions and are, therefore, ideally suited for use with formulations containing water-unstable drugs.*



*Artwork by Peter Fielder-Shaw.*

***Toshihiro Ogura,* Yoshihiro Furuya and Seinosuke Matsuura***

Hard capsules were developed as an edible container to mask the taste and odour of medicines. As a result of the introduction of mass-production techniques and high-speed capsule filling machines, capsules have become one of the most popular dosage forms for pharmaceuticals. Capsules have traditionally been used for powder or granule formulations, but in recent years have been adapted to contain oily liquids, tablets and even powders for inhalation. Capsules enjoy widespread popularity because of their relative ease of manufacture (compared with other dosage forms such as tablets) and flexibility of size to accommodate a range of fill weights. They are readily able to achieve bioequivalence between different strengths of the same formulation.

Capsules do have some drawbacks. Capsule shells made from gelatin, the main material used for this purpose, generally contain 13–15% water and therefore may not be suitable for use with readily hydrolysable drugs. Some drugs may react with the amino groups of gelatin, causing discolouration or formation of crosslinks between gelatin molecules, which retard capsule dissolution. Gelatin products are sometimes shunned as a result of religious or vegetarian dietary restrictions.

For these reasons, work is under way to develop capsules made of starch, cellulose or polyvinyl alcohol/vinyl acetate mixtures. Yamamoto *et al.* recently succeeded in making capsules from hydroxypropyl methylcellulose 2910 (HPMC),[1] a material also used as a water-soluble film coating. We have confirmed the applicability of the HPMC capsule to products.[2] As *USP*, *EP* and *JP* (the United States, European and Japanese pharmacopoeia) monographs all describe capsules made of cellulose or methylcellulose, in addition to gelatin, the HPMC capsule conforms to pharmacopoeial standards.

## Manufacturing HPMC capsules

HPMC capsules can be manufactured by the dipping and forming method, employed for the manufacture of hard gelatin capsules. Shaped pins are dipped into a solution of HPMC, after which the HPMC film is gelled, dried, trimmed and removed from the pins. The body and cap pieces are then joined. As HPMC alone does not gel at low temperatures — temperatures greater than 60 °C are required — small amounts of carrageenan, a natural gelling agent widely used in the food industry, and potassium chloride, a gelling promoter, are added.

## Physical characteristics of HPMC capsules

The HPMC capsule is odourless and flexible, and exhibits similar dissolution behaviour to the gelatin capsule. Its appearance is the same, except that it lacks the lustre of gelatin. The physical properties of both HPMC and gelatin capsule shells that may affect stability and dissolution, and therefore their suitability for use with various formulations and intended use, are listed in Table I.

**Capsule hardness.** There are two components of capsule shell hardness — brittleness and tolerance to deformation — which determine suitability for use with automated encapsulating machines, as well as end use. When the moisture content of the capsule shell is decreased, as may occur when a desiccant is added to a package of capsules

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containing moisture-labile drugs, gelatin capsules tend to become brittle and are subject to breakage during transport and storage. The relationship between brittleness and moisture content can be determined using a hardness tester (Figure 1). The results of our testing show that the percentage of broken gelatin capsules sharply increases as the moisture content of the hard gelatin shell drops below 10%, although the degree of brittleness can be modified somewhat by addition of polyethylene glycol (PEG) during manufacture. In contrast, no brittleness was observed in HPMC capsule shells even at moisture levels of only 2% (Figure 2a).

Tolerance of the capsule shell to denting or deformation was estimated, using the same testing device, by determining the falling distance necessary for a 7 g weight to cause deformation in 50% of the capsules tested. As can be seen in Figure 2b, tolerance (resistance) of both types of capsules to deformation increased with decreasing moisture content. The two types of capsules show equivalent tolerance to deformation at their average moisture content levels — 2–5% for HPMC capsules and 13–15% for gelatin capsules.

**Performance during test runs on a capsule filling machine.** Results of the hardness testing suggested that HPMC capsules would be acceptable for use with automated capsule filling machines. Capsule filling tests were conducted with encapsulators, the results of which are summarized in Table II. Filling defects, such as deformation, splits, dents or cracking, occurred at frequencies of less than 0.03%, a rate similar to that observed when filling hard gelatin capsules.

## Biopharmaceutical characteristics

Cephalexin, which is mainly absorbed from the duodenum, was used as the model formulation to compare capsule dissolution and drug absorption from gelatin and HPMC capsules.

**Dissolution from capsules.** Dissolution testing (Figure 3) was performed with solutions of various pHs using the paddle method described in the *JP*. Results of testing in the *JP* 'first test fluid' (pH 1.2) and a solution of pH 4 (Figures 3a and b) showed no significant differences in the dissolution behaviour of either type of capsule. When using the *JP* 'second test fluid' (pH 6.8; Figure 3c), both types of capsules achieved approximately 100% dissolution. Dissolution times for the HPMC capsule, however, were approximately 5 min longer than those for the gelatin capsule, because of the formation and persistence of a very friable gel membrane surrounding the drug fill. The presence of potassium, a known promoter of carrageenan gelation, in the *JP* second test fluid was suggested to be the cause of this membrane formation.

Subsequent testing of the two capsule types in various buffer solutions (pH 6.8) that did not contain potassium or in plain distilled water showed no difference in dissolution times, thus supporting our hypothesis (Figure 3d). As the cation concentration in the gut is low, test solutions that do not contain potassium, such as McIlvaine buffer (pH adjusted over a range of 3.0–7.5 by addition of up to 0.05 M disodium hydrogen phosphate and 0.025 M citric acid), or one of the pH 6.8 test solutions listed in the *USP* for enteric formulations, might be considered acceptable alternatives for determining rates of dissolution.

**Human studies of cephalexin rates of absorption from HPMC and gelatin capsules.** HPMC and gelatin capsules containing 250 mg of cephalexin, together with 100 mL of water, were administered to six healthy

**Table I:** *Physical properties of capsule shells made of HPMC and gelatin.*

| | HPMC | Gelatin |
|---|---|---|
| Moisture content | 2–5% | 13–15% |
| Water vapour permeability | Low | Low |
| Substrate for protease | No | Yes |
| Maillard reaction with drug fill | No | Yes |
| Deformation by heat | Above ~80 °C | Above ~60 °C (degradation) |
| Water dissolution at room temperature | Soluble | Insoluble |
| Static | Low | High |
| Light degradation | No | Possible |

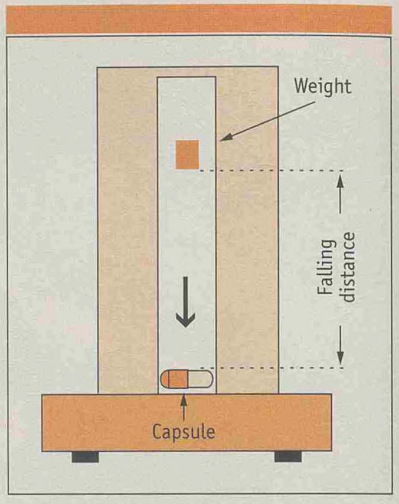


**Figure 1:** *Hardness tester for capsules.*

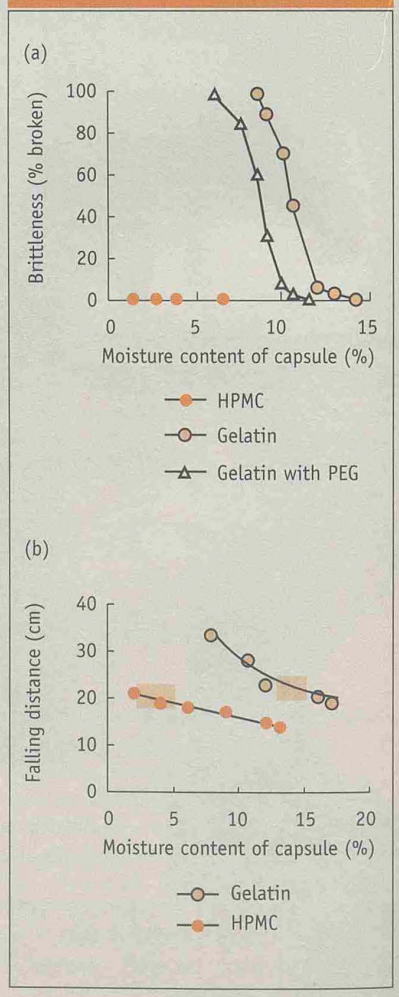


**Figure 2:** *Test results of mechanical integrity of HPMC and gelatin capsules at various levels of moisture content. (a) Brittleness; falling distance of a 50 g weight is 10 cm. (b) Tolerance to deformation; falling distance of a 7 g weight, deforming 50% of capsules.*

**Table II:** *Performance of encapsulators with HPMC capsules.*

| Capsule filling machine | | Capsule size | Speed (capsules/h) | Outcome (capsules) | Defect rate (%) |
|---|---|---|---|---|---|
| Höfliger and Karg | GKF1000 | 1 | 36000 | 120000 | <0.001 |
| Höfliger and Karg | GKF1000 | 1 | 60000 | 500000 | 0.001 |
| Harro Höfliger | KFM1 | 1 | 3600 | 3000 | <0.03 |
| Shionogi Qualicaps | LIQFIL super80 | 1 | 80000 | 40000 | <0.003 |

volunteers under fasting conditions, and drug plasma concentrations were determined. As illustrated in Figure 4, drug concentration profiles were similar, and no significant differences were observed in total drug absorbed (AUC, area under the plasma level curve), peak plasma concentrations ($C_{max}$) or time to reach peak plasma concentrations ($t_{max}$).

## Application to formulations

Some drugs react with gelatin, which may prolong dissolution or result in discolouration of the capsule shell during storage. Other drugs become hydrolysed by the moisture contained in the gelatin capsule shell. HPMC is not only chemically inert, but has a lower moisture content (2–5%), permitting maintenance of a low humidity environment within the HPMC capsule shell.

**Addressing potential prolonged dissolution problems.** Drugs containing aldehyde groups, or producing aldehydes on decomposition, promote crosslinking between gelatin proteins,[3] forming a thin insoluble membrane called a pellicle[4] that may delay dissolution. If the membrane is disrupted by the mechanical forces of gastric emptying or is broken down by digestive enzymes, its formation would not affect absorption and bioavailability of the drug. The US Food and Drug Administration (FDA)/Industry Gelatin Capsule Working Group, in fact, concluded that formation of an insoluble membrane could be considered to have a negligible impact on drug bioavailability if the capsules dissolved during the 'two-tiered dissolution test,' which employs a medium containing digestive enzymes.[5]

**Table III:** *Disintegration test results of HPMC and gelatin capsules filled with a macrolide antibiotic and stored at 60 °C, 75% RH for 10 days.*

| | Disintegration time (min) | |
|---|---|---|
| | Initial | At day 10 |
| HPMC capsule | 4.6 | 4.5 |
| Gelatin capsule | 3.3 | >30 |

Pellicle formation, however, still represents the potential for dissolution problems, and investigations are under way to find stabilizers that would prevent formation of crosslinks between gelatin molecules. A practical alternative is to employ HPMC capsules as a means to completely avoid the formation of insoluble membranes. Matsuura and his team have demonstrated the value of this approach by filling both hard gelatin and HPMC capsules with spiramycin, a macrolide antibiotic known to cause insolubilization of gelatin capsules.[6] After storage for 10 days under conditions of 60 °C and 75% relative humidity, the gelatin capsules did not disintegrate, whereas the HPMC capsules were unaffected (Table III).

**Addressing potential discolouration problems.** Capsules filled with substances containing aldehyde groups, such as ascorbic acid, will become brown by discolouration under high temperature/humidity conditions. This is thought to be the result of a reaction between ascorbic acid and the α-amino group on the gelatin protein, as depicted in Figure 5. To minimize discolouration reactions with these types of substances, either the moisture content of the gelatin capsule shell must be lowered and/or the capsules must be stored in moisture-proof containers.

HPMC does not contain reactive groups, thereby minimizing discolouration problems that occur as a result of interactions between the drug and capsule shell. To confirm this,

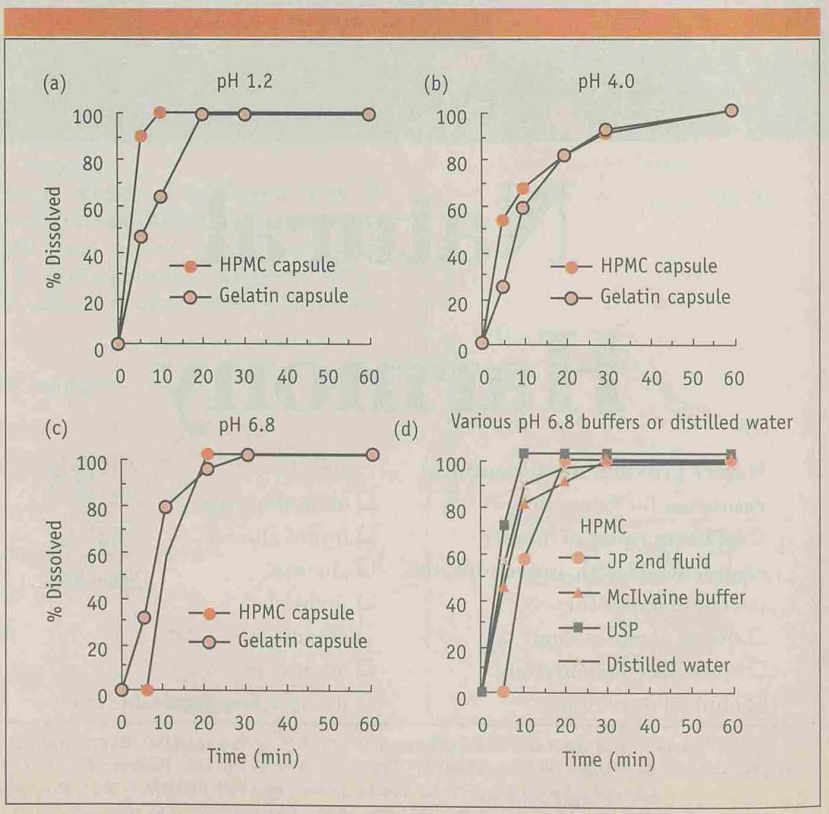


**Figure 3:** *Comparison of dissolution of cephalexin in various media from HPMC and gelatin capsules*

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