DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 12(11-13), 2113-2126 (1986)

THE INJECTION-MOULDED CAPSULE [1]

L. Eith, R.F.T. Stepto, I. Tomka*, F. Wittwer

[2] Capsugel AG, Engelgasse 11, CH-4010 Basel, Switzerland and
* Institut für Polymere, ETH-Zentrum, CH-8092 Zürich, Switzerland

ABSTRACT

The paper describes the development of the first injection-moulded pharmaceutical capsules. Starch and gelatin capsules have been prepared and the processing conditions and properties of the resulting starch capsules are considered in detail. Comparisons are made between the processing of thermoplastics and starch and gelatin and the starch capsule is compared with the conventional, dip-moulded hard gelatin capsule.

INTRODUCTION

The use of gelatin for the production of pharmaceutical capsules has now been established for more than a century, although Lehuby made starch capsules in 1846. The traditional, dip-moulding process by which gelatin capsules are prepared has undergone many improvements. It employs approximately 30% aqueous solutions of gelatin with the subsequent removal by drying of the greatest part (90%) of the water from the shaped, half-finished product. The drying is time-consuming and involves high production costs. In addition, the handling of aqueous gelatin solutions at 40 - 50° C raises the probability of bacterial growth.

 0363-9045/86/1211-2113$3.50/0

The drying procedure is obviated if the water content of the starting material and the end-product are the same and remain constant during processing. In principle, the constancy of water content can be achieved by producing hard capsules using thermoplastics processing techniques. The size and shape of the product and the constancy of water content define injection moulding as the preferred technique. At the same time, injection moulding gives a product with precise dimensions.

Recent investigations have shown that it is possible to form gelatin and starch capsules by injection moulding. The injection-moulded capsule is not only a step-forward in capsule production, but also in polymer processing technology. It is the first use of elevated temperatures to injection mould native polymer materials having high water contents into stable shaped articles.

The present paper describes the development of injection-moulded starch and gelatin capsules and concentrates in particular on the processing conditions and properties of the resulting starch capsules.

THE INJECTION MOULDING PROCESS

Injection moulding is widely used for processing so-called thermoplastic polymers; those which, on heating, form a melt of high viscosity (typically 10^3 to 10^5 Pa s, i.e. 10^4 to 10^6 P at processing temperatures). It is also sometimes used for processing thermosetting materials; those which react on heating.

The process may be described[3] with reference to fig 1, which is a schematic drawing of the polymer-processing parts of a conventional injection-moulding machine. Solid polymer in the form of a powder, or, more usually, granules or pellets is fed through the hopper onto a rotating, reciprocating screw. The feed material moves along the screw towards the tip. During this process, its temperature is increased by means of external heaters around the outside of the barrel and by the shearing action of the screw.

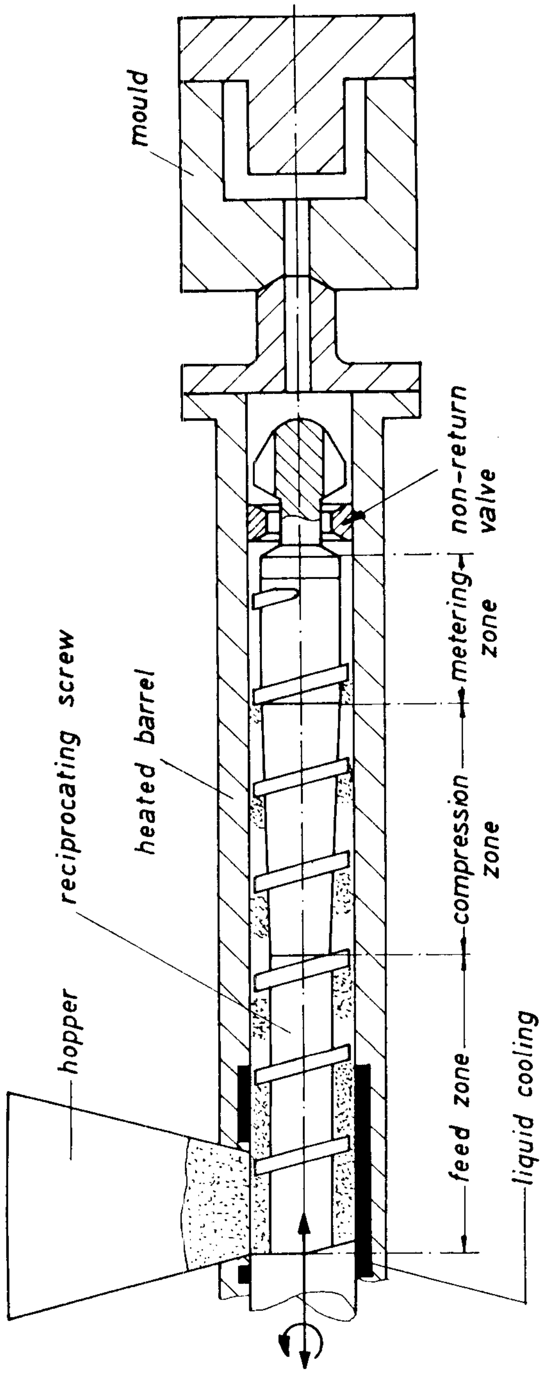

FIGURE 1

Schematic representation of the polymer-processing parts of a screw-fed injection-moulding machine. As indicated, the screw undergoes reciprocating action (axial translation) as well as rotation.

Starting in the feed zone and continuing in the compression zone, the particulate feed becomes gradually molten. It is then conveyed through the metering zone, where homogenisation of the melt occurs, to the end of the screw. Notice that, over the compression zone, the diameter of the core of the screw increases towards the tip. Thus, the feed is compressed as it is transported. The compression is important for providing friction to aid melting and for the exclusion of air from the particulate feed in order to obtain a homogeneous melt.

Whilst the screw is rotating, the exit from the barrel to the mould is closed, either through a shut-off nozzle or by solidified, previously injected material. Hence, melt transported to the end of the screw must be accommodated within the barrel beyond the non-return valve. To enable this to occur the screw moves backwards as it rotates. This 'reciprocating', axial movement takes place against a predetermined, hydraulic back-pressure which also aids the uniformity of feed and homogeneity of melt.

When sufficient melt has collected for injection of the next shot, rotation of the screw stops whilst the polymer in the mould finally cools sufficiently for the mould to be opened and the moulded part or parts ejected. The mould then closes and the screw moves forward quickly under high pressure, injecting molten polymer and refilling the mould cavities. Pressures between 700 - 2000 bar are used in the injection part of the cycle and the non-return valve at the end of the screw ensures that melt does not flow back along the screw during injection.

Throughout the process, the mould is kept below the glass-transition or melting temperature of the polymer. As polymer is cooling in the mould, the gate or entrance to the mould contains melt which is kept under a holding pressure. Thus, the melt in the mould contracts and becomes compressed by the relatively slow injection of a small volume of melt. Injection continues until the material in the gate has solidified. The screw then commences rotation and backward axial movement to start the next cycle. The conditions of secondary injection are so arranged that the mould is finally filled with the correct amount of solid material.

The injection moulding cycle is summarised in fig 2. The time for a complete cycle is usually a few seconds.

Thermoplastics

Table 1 gives examples of the temperatures used for the injection moulding of some common thermoplastics in relation to their melting and glass-transition temperatures. The temperature of the melt in the barrel is always higher than T_m for crystallisable polymers and higher than T_g for non-crystallisable polymers (e.g. polystyrene). The higher the temperature of the melt, the lower is its viscosity and the easier is flow and mould filling. However, the temperature is limited, as degradation of the polymer must be avoided and solidification in the mould should not take too long. Antioxidants are sometimes added against degradation and plasticisers to aid flow. The temperature in the mould dictates the rate of cooling and complete filling should be achieved before solidification starts. In addition, the structure of the material formed is affected by the cooling rate. To aid ejection of the moulded part, mould-release agents are sometimes used as additives to the feed or are sprayed onto the surfaces of the mould cavities. They reduce adhesion between the moulded part and the mould.

Capsules from Starch and Gelatin

The material of which a hard capsule is to be made must be edible and have a dissolution/disintegration behaviour which gives satisfactory bioavailability of its contents. In addition, to be processed by injection moulding, the material used must have properties consistent with the requirements of the process, namely:

- melt formation at the processing temperature without the onset of thermal degradation

- the melt should have a viscosity which allows the mould to be filled at the injection pressure used

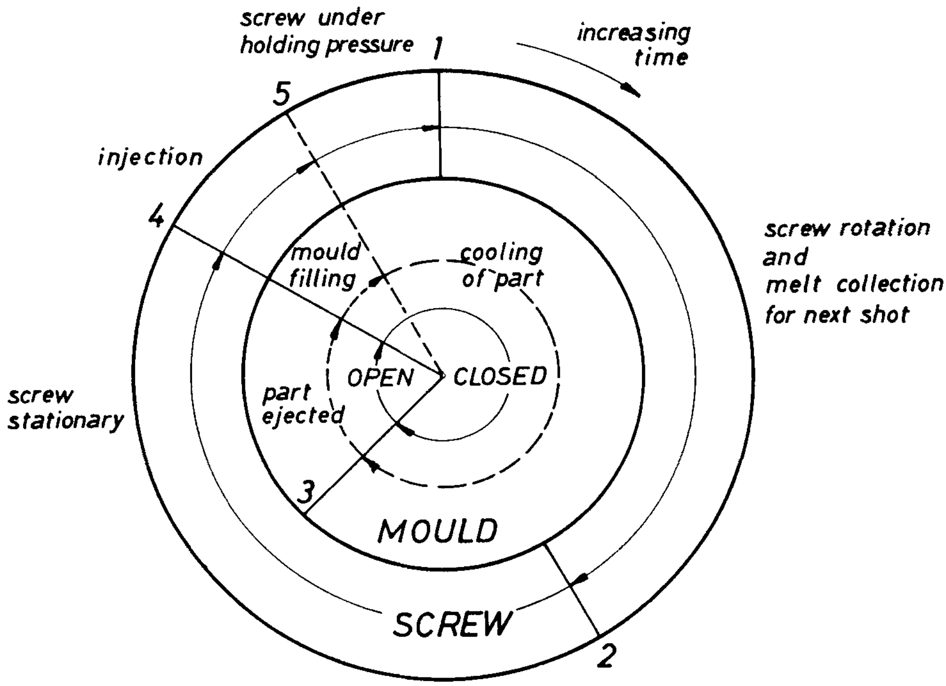

FIGURE 2

Summary of the injection-moulding cycle, showing synchronisation of screw and mould operations.

	Screw	Mould
1 → 2	rotation and backward movement	closed : cooling of moulded part
2 → 3	stationary: collected melt in front of screw	closed : cooling of moulded part
3 → 4	stationary: collected melt in front of screw	opened → moulded part ejected → closed
4 → 5	forward movement under injection pressure	closed : mould fills with melt
5 → 1	slow secondary injection under holding pressure	closed : filling completed, moulded part starts cooling

TABLE 1

Temperatures used for the injection moulding of thermoplastics

Polymer*	Melt Temp/° C	Mould Temp/° C	T_g/° C	T_m/° C
LDPE	180 - 250	20 - 40	- 110	115
HDPE	220 - 300	20 - 60	- 110	134
PP	230 - 280	20 - 60	- 10	165
PS	170 - 280	10 - 60	90 - 100	-
Nylon 6,6	260 - 290	40 - 90	50	240

* LDPE - low-density (branched) polyethylene; HDPE - high-density polyethylene; PP - polypropylene; PS - polystyrene.

- mould release should occur without plastic deformation or rupture of the product
- the moulded capsule must be sufficiently strong for satisfactory filling and stability of shape during subsequent use.

With starch and gelatin, the amount of water present markedly affects processing properties. In this respect, the water adsorption behaviour is of prime importance. Fig 3 shows that the gelatin/water[4,5] and starch/water systems[6] have similar adsorption isotherms. For both systems in fixed volumes, the phase separation of pure water does not occur on raising the temperature. Even at temperatures higher than 100° C this was found to be true. In addition, it was found that injection moulding was possible as gelatin/water and starch/water mixtures of equilibrium water content at ambient temperatures and humidities (13 - 14%) gave materials which flowed satisfactorily without degradation in the temperature range 140 -190° C.

At this point, an essential difference between the injection moulding process and the dip-moulding process for gelatin should be remembered. The slow drying of the gelatin/water mixture to 13 - 14% water in the dip-

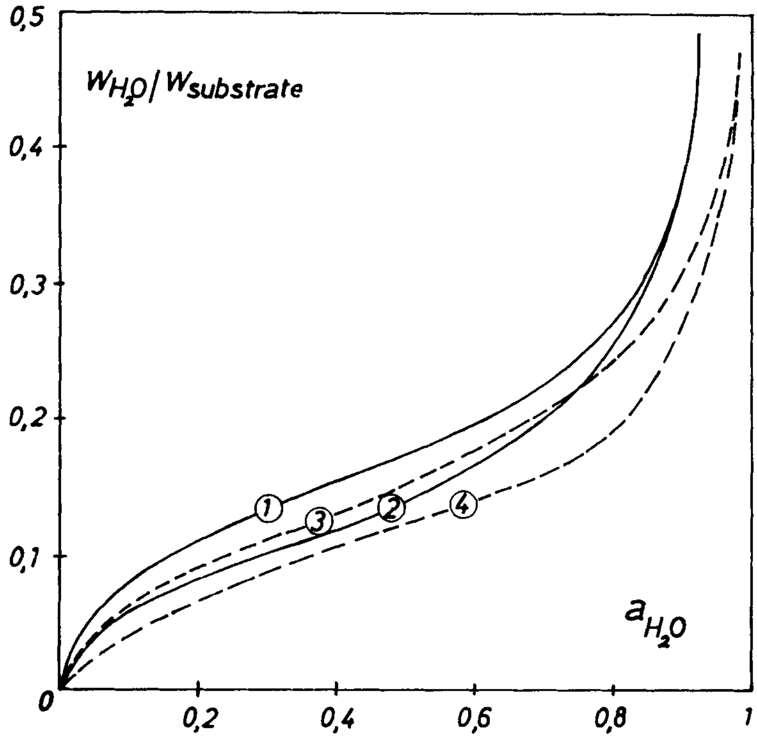

FIGURE 3

Adsorption isotherms of the gelatin/water[4,5] and starch/water systems[6]. Curves: 1. gelatin 20° C; 2. gelatin 60° C; 3. starch 20° C; 4. starch 67° C.

moulding process allows fibrils to form[7]. As stated, this amount of water corresponds to that given by the adsorption isotherm for ambient conditions (curve 1, fig 3). The fibrils give a network structure to the material, endowing sufficient rigidity and toughness at ambient temperatures. With the more rapid, injection-moulding process, the melt of gelatin/water at 13 - 14% water sets to an amorphous material at room temperature. Fig 4 shows the variation of glass-transition temperature (T_g) with water content for the gelatin/water[7] and starch/water systems. In particular, at room temperature and 13 - 14% water both systems are about 25° C below T_g.

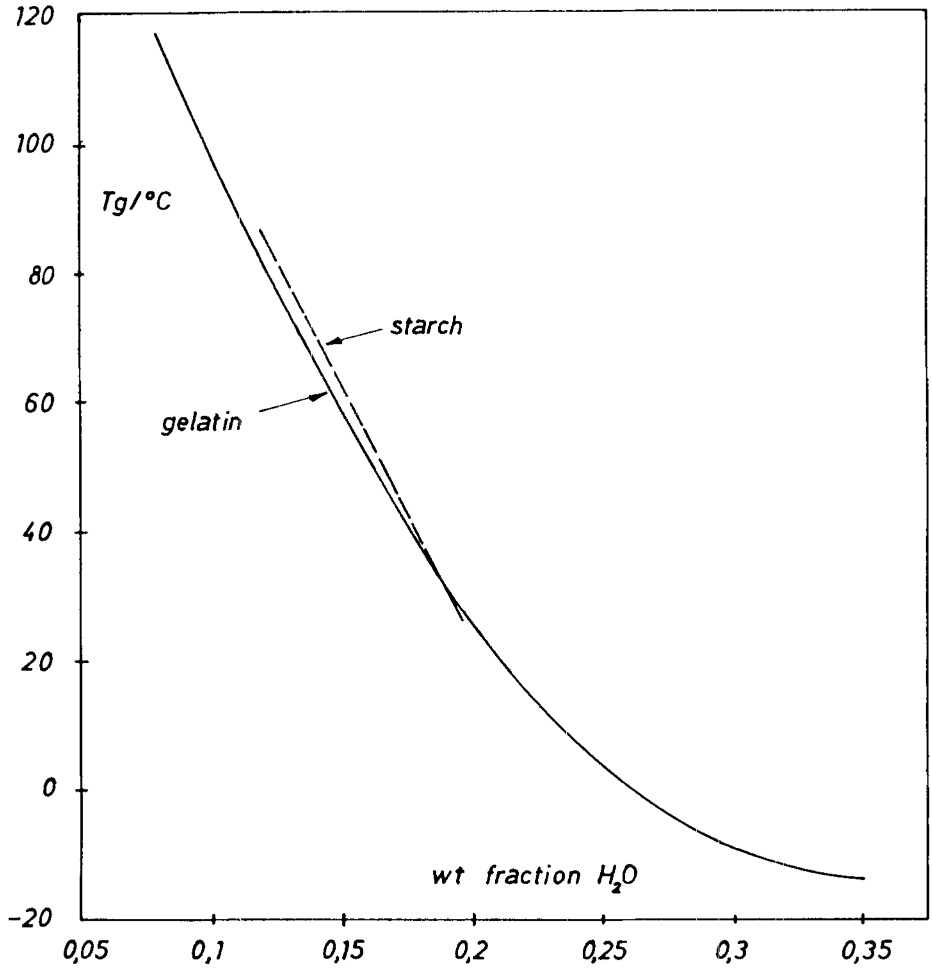

FIGURE 4

Glass-transition temperatures (Tg) versus water content for the gelatin/water[7] and starch/water systems.

An advantage of the injection moulding process is that it easily allows the wall thickness and, hence, capsule strength to be improved, even below T_g. With thicker walls, capsules would be expected to show increased times of disintegration and dissolution. However, thicker-walled starch capsules (0.4 mm) were found to behave satisfactorily. Thus, an increased wall thickness leads to good capsule properties, for example, handling (filling and blistering) and drug-release.

Starch Processing Conditions

The injection moulding of starch presents problems which are to some extent similar and to some extent different from those conventionally encountered with thermoplastics. By the control of the water content and of the temperature changes along the barrel, the starch granules must be broken down to form a melt. The water content must remain constant and be kept as low as possible, but be sufficient for homogeneous melt formation before degradation. The extrusion cooking of starch, for example, as in the processing of food, leads to materials of inferior mechanical properties.

Compared with thermoplastics, irreversible physico-chemical changes occur during processing, so that closer control of cycle time and water content, as well as temperature, is recommended. Further, additives may be used to aid flow and mould release.

DESIGN AND PRODUCTION OF INJECTION-MOULDED CAPSULES

To date, most of the processing has been directed towards the manufacture of capsules, and multi-cavity cap moulds and body moulds have been developed. They allow the separate production of caps and bodies. The separate manufacture of caps and bodies means more flexibility in production. The same-sized cap can be used with different lengths of body to produce, for example, size 1 and size 4 capsules.

Fig 5 shows the design of an injection-moulded capsule together with that of a hard gelatin capsule. It is immediately apparent that a smaller closure area be used with the injection-moulded product. This is because the dimensions can be much more closely controlled in injection moulding than in dip moulding.

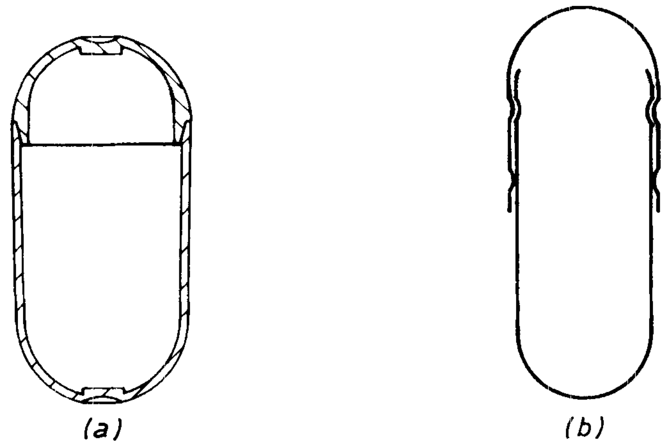

FIGURE 5

(a) Injection-moulded capsule.
(b) Coni-Snap™, hard gelatin capsule

External, linear dimensions of caps and bodies of the starch capsule are constant to better than 0.1 mm and wall thicknesses to even less. Cap and body can be joined by a tamper-resistant, snap connection to give a smooth surface to the capsule.

Because, in contrast to a dip-moulding process, the injection-moulding process is not restricted to particular shapes of article, other products applicable to drug and food delivery can be produced just as easily. In addition, injection-moulded starch and gelatin materials have many other possible applications in the engineering-plastics area.

PROPERTIES OF STARCH CAPSULES

Filling-Machine Behaviour

Apart from matters of good design, the successful behaviour of capsules on filling relates primarily to the capsule material being sufficiently tough and rigid to survive impact without permanent deformation. Tests have shown that the injection-moulded starch capsule easily meets these requirements. In addition, because caps and bodies are made separately, it has been possible to use a simpler design of filling machine.

Particular Features of Starch Capsules

The injection-moulded starch capsule or container has the following advantageous features regarding design, properties and application:

1. The possibility of moulding many different shapes and closure systems, and also subdividable capsules.

2. Capsules are reproducible in size and properties.

3. No lengthy drying process is required.

4. Good stability under extreme temperature/humidity conditions.

5. No bacterial problems during manufacture; no preservatives are used and no toxic residues remain from dead microbial bodies.

6. Capsule design is excellent for coating, e.g. for enteric and controlled-release applications.

7. Wall thickness can be varied, allowing more controlled release.

8. Larger capsules are easily manufactured, e.g. for veterinary applications.

9. Embossing and debossing can be included as part of the mould-cavity design; no separate imprinting stage is necessary.

10. Good oesophagus gliding.

11. The starch capsule is a natural-looking product having an excellent image for the health-food, herbal and dietetic markets.

12. Starch as a plant polymer is ideal when religious or dietetic considerations are important.

13. The basic raw material is cheap.

Comparative Behaviour of Starch Capsules

Comparative disintegration and bioavailability studies of starch capsules (0.4 mm wall-thickness) and conventional, dip-moulded hard gelatin capsules have been carried out. The results are summarised in table 2. The starch capsule behaves satisfactorily. Disintegration is slower but in vivo bioavailability is faster. In addition, the properties of the injection-moulded capsule may easily be modified by changing wall thickness and by the incorporation of additives in the formulations for injection moulding. Due to the high temperatures used, the injection moulding process has the further

TABLE 2

Comparative behaviour of hard gelatin and starch capsules. Values quoted are mean values from 6 - 10 determinations.

Capsule	Disintegration[8] /min	Bioavailability:[9] plasma concentration of mefenamic acid after 1 h/ g cm^{-3}
Hard gelatin (0.1 mm wall thickness)	1	3.8
Starch (0.4 mm wall thickness)	4	5.3

advantage that bacterial and fungal growth in the processed material is negligible.

SUMMARY

The injection moulding of gelatin and starch of fixed water content to make capsules has been investigated. Injection moulding gives capsules which are reproducible in dimensions and properties. Their drug-delivery behaviour compares well with that of hard gelatin capsules.

The use of injection moulding means that the encapsulation shape is no longer so restricted as in dip-moulding and it is possible to develop other, biodegradable drug- and food-delivery containers.

ACKNOWLDGEMENTS

The authors wish to acknowledge the assistance of B. Dobler, G. Lay, K. Pyrah and M. Thoma (Capsugel), T. Raible (ex Capsugel), P. Wippenbeck (FH Aalen) and P. Yeh (ETH) in the development of the injection-moulded capsule.

REFERENCES

1. The injection-moulded starch capsule will be marketed under the name CAPILL.
2. To whom correspondence should be addressed.
3. See, for example, Z. Tadmor and C.G. Gogos, Principles of Polymer Processing, Wiley-Interscience, John Wiley + Sons, Inc., New York, 1979
4. D. Gehrmann, Dissertation, Darmstadt, 1979
5. I. Tomka, Chimia 1983, 37 33
6. C. van den Berg, Ph.D. Thesis, Landbouwhogeschool, Wageninge, 1981
7. I. Tomka, H. Bohonek, A. Spühler and M. Ribeaud, J. Phot. Sci 1975, 23 97
8. According to German Pharmacopoeia (DAB 8).
9. Human bioavailability from 250 mg charges of Ponstan in capsules.