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Preparation and characterization of novel fast disintegrating capsules (Fastcaps) for administration in the oral cavity

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Abstract

The objective of this study was to prepare novel capsule-based fast disintegrating dosage forms for the oral cavity (Fastcaps). First, cast films were prepared from various additive-containing gelatin solutions and evaluated with respect to disintegration time and mechanical properties in order to identify suitable formulations for the capsule preparation. The disintegration time of films decreased with decreasing bloom strength and could be further decreased by the addition of sugars or PEGs. Fast disintegrating capsules were successfully prepared by a dipping process, whereby parameters such as the viscosity and temperature of the dipping solution and the dipping velocity of the steel pins were optimized. The required viscosity range of the dipping solution for Fastcap manufacturing was 500–600 cP. The addition of the hydrophilic additives (xylitol, sorbitol or PEG 1500) did not significantly affect the viscosity and gelation temperature of the dipping solution. The in vitro disintegration of Fastcaps (30–45 s) was twice as rapid as the one of regular hard gelatin capsules. In vivo, Fastcaps disintegrated rapidly (9–13 s) and their content was spread throughout the oral cavity within seconds. Lactose and/or microcrystalline cellulose were suitable fillers for Fastcaps. The mechanical properties of Fastcaps were similar to commercially available gelatin capsules, which assures good processability and handling.

Keywords: Gelatin films; Capsules; Fast disintegrating dosage forms; Oral cavity

1. Introduction

Solid dosage forms designed for rapid disintegration in the mouth have recently received much attention (Charman and Charman, 2002). Advantages of oral fast-disintegrating dosage forms includes: (1) the administration to patients who cannot easily swallow, such as the elderly, stroke victims, healthcare facility and bedridden patients and patients who refuse to swallow, such as pediatric, geriatric and psychiatric patients (Wilson et al., 1987; Fix, 1998); (2) more rapid drug absorption, as evident in one bioequivalence study (Selegiline) through pre-gastric absorption from the mouth, pharynx and esophagus (Fix, 1998); (3)

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convenience and patient compliance (people, who do not have ready access to water) (Fix, 1998); (4) product differentiation, line extension and life-cycle management, exclusivity of product promotion and patient-life extension (Virely and Yarwood, 1990).

Several platform technologies based on fast-disintegrating dosage forms have been developed, such as freeze-dried tablets (Zydis®), compressed fast-disintegrating tablets (Orasolv®, Durasolv®, Wowtab®, FlashDose®) and fast-dissolving films (Listerine® Pocketpacks).

The Zydis™ dosage form was developed by Scherer; it dissolves within 3–5 s in the oral cavity (Seager, 1998; Kearney, 2002; Clarke et al., 2003). Products on the market include Zyprexa® Zydis®, Maxalt-MLT® and Romeron® SolTabs®. This dosage form is produced by freeze-drying aqueous drug/excipient suspension/solutions within blister packs (Corveleyn and Remon, 1997). The final product is a dried, sponge-like tablet in a special peel-off blister pack (Smith et al., 2001). Major disadvantages of the Zydis® technology is the time-consuming freeze-drying process, the limitation to low dose drugs, the poor mechanical properties and moisture sensitivity.

Other marketed fast-disintegrating dosage form technologies are based on conventional tabletting method. The Orasolv™ technology is based on an effervescent mixture and taste-masked coated or microencapsulated drugs (Pather et al., 2003). The Shearform™ technology is based on a floss-like matrix (Sastry, 2000). The floss is a fibrous material similar to cotton-candy fibers, commonly made of saccharides such as sucrose, dextrose, lactose and fructose (Cherukuri, 1996). The compression force used for such tablets is relatively low. The resulting tablets are soft, friable and highly moisture sensitive (Habib et al., 2000).

Fast disintegrating intraoral films represent another dosage form in the pharmaceutical area. They differ from the other types of fast disintegrating dosage forms with regard shape/appearance and manufacturing process. An oral care product Cool Mint Listerine® PocketPaks® has been introduced based on this film technology. The water soluble films are moisture sensitive; in addition, the drug loading capacity of fast disintegrating films is perhaps the lowest among all fast disintegrating dosage forms.

Table 1
Comparison of Fastcaps to other fast disintegrating dosage forms for the oral cavity

Parameter	Fastcaps	Zydis®	Tablets	Films
Wide range of actives	Yes	No	?	No
High drug loading	Yes	No	?	No
Taste-masked particles	Yes	No	?	No
Modified release particles	Yes	No	?	No
Stability	Yes	?	Yes	?
Semisolid, liquid formulations	Yes	No	No	No
Special packaging	No	Yes	?	Yes

In this study, a new type of fast-dissolving drug delivery system based on gelatin capsules was developed (Bodmeier, 1999). In contrast to conventional hard capsules, the capsules developed in this study (Fastcaps) consist of gelatin of low bloom strength and various additives to improve the mechanical and dissolution properties of the capsule shell. The advantages of these fast disintegrating capsules are high drug loadings, possible solid and liquid fillings, no compression of coated taste-masked or extended release drug particles/pellets, good mechanical properties, simple manufacturing, mechanical stability and no requirement of special packaging (Table 1).

The objectives of this study were to develop a simple and reproducible preparation technique for these capsules and to characterize the properties of the Fastcaps in comparison to conventional hard gelatin capsules.

2. Materials and methods

2.1. Materials

Size 0 or 1 hard gelatin capsules (HGC), size 0 hard gelatin capsules containing polyethylene glycol (PEG HGC), size 0 hydroxypropyl methylcellulose capsules (HPMC) (Shionogi Qualicaps Ltd., Nara, Japan), gelatin (type B) granules with bloom strengths of 43, 80, 100, 180 and 260 (approximate moisture content 11%) (DGF Stoess Deutsche Gelatin Fabriken Stoess AG, Eberbach, Germany), polyethylene glycol 400, 1500 and 4000 (PEG, BASF, AG Ludwigshafen, Germany), cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®, FMC Co., Brussels, Belgium) micro-

crystalline cellulose (Avicel® type PH101 FMC Co., Brussels, Belgium), sodium carboxymethylcellulose (Tylopur®, C600, Clariant GmbH, Wiesbaden, Germany), sodium starch glycolate (Explotab®, Pennwest, Patterson, NY, USA), sorbitol (Caesear & Loretz GmbH, Bonn-Beuel, Germany), xylitol (C*Xylidex, Caesear & Loretz GmbH Bonn-Beuel, Germany), lactose [D(+)-lactose monohydrate, Riedel-de Haën AG, Seelze Germany], citric acid (Sigma–Aldrich Chemie GmbH, Deisenhofen, Germany) and saccharose (Merck AG, Darmstadt, Germany).

2.2. Preparation of gelatin films

Aqueous solutions of gelatin of different bloom strength (43, 80, 100, 180 and 260) and of conventional hard gelatin capsules were prepared at concentrations of 10–20% (w/w). PEG, sorbitol or xylitol were added to achieve a faster disintegration and better film properties. These solutions were cast onto Teflon covered glass plates (14 cm × 14 cm) and dried at ambient conditions. The film thickness ($108 \pm 10\,\mu m$) was measured at five points with a thickness gauge Minitest 600 (Erichsen GmbH & Co. KG, Hemer, Germany). The films were stored at ambient conditions until equilibrated and were then evaluated with respect to their disintegration time, mechanical strength and moisture uptake characteristics.

2.3. Mechanical properties of gelatin films

The mechanical properties (puncture strength, elongation and elastic modulus) were investigated with an Instron® Testing Machine 4466 (Wolpert, GmbH, Darmstadt, Germany) equipped with a 500 N load cell. The film was placed in a holder with a cylindrical hole ($r = 1.1$ cm) and a metal probe (diameter, 5 mm; length, 15 cm) was then driven at a speed of 5 mm/min through the film. Force (N)–displacement (mm) curves were recorded.

The following parameters were calculated (Bodmeier and Paeratakul, 1993; Radebaugh et al., 1988):

$$\text{puncture strength} = \frac{F_{max}}{A_{CS}}$$

where F_{max} is the maximum applied force at film break, A_{CS} the cross-sectional area of the edge of the film located in the path of the cylindrical hole of the film holder, with $A_{CS} = 2r\delta$, where r is the radius of the hole and δ is the thickness of the film:

$$\text{elongation}\,(\%) = \left[\frac{[(r^2 + D^2)^{1/2} - r}{r}\right] \times 100$$

where r is the radius of the film exposed in the cylindrical hole of the film holder and D represents the displacement of the probe from the point of contact to point of puncture:

$$\text{modulus at puncture} = \frac{\mathrm{d}\left(\frac{F}{A_{cs}}\right)}{\mathrm{d}(\%\,\text{elongation})}$$

where F is the applied force.

2.4. Viscosity of the gelatin solutions

The viscosity of various gelatin solutions was measured with a rotational viscometer (Haake RH101, Thermo Haake GmbH, Karlsruhe, Germany) with a parallel plate and cone (20 mm in diameter and 4° angle) at a constant shear rate ($80\,s^{-1}$). The gelatin solutions (12.5–35.0%, w/w) were equilibrated for not longer than 1 h at measuring temperatures of $40–60 \pm 1\,^{\circ}C$ in a water bath prior to measurement. The sol–gel transition temperature of the gelatin solutions was obtained from the viscosity versus temperature profile over the temperature range of 30–60 °C.

2.5. Preparation of fast disintegrating capsules

The capsules were prepared on a laboratory scale dipping process with stainless steel pins (size # 1). The pins were dipped into a warm gelatin sol, followed by elevation and rotation of the gelatin covered pins in air to set the gelatin solution. The pin bars were then placed in a chamber (gently heated by hair drier) at 25–30 °C for 30–60 min (depending on the formulation). The capsule shells contained approximately 15–18% (w/w) water after removal from the chamber, which was necessary for the trimming process.

The gelatin sol contained 35% (w/w) gelatin, 0.15% methylparaben as preservative and 64.85% distilled water. 15% xylitol or sorbitol or 5% PEG (w/w, based on gelatin) were added to this solution. The gelatin sol temperature, the dipping time as well as the drying process were adjusted for the different types of gelatin

Table 2
Dipping conditions for solutions of gelatin of different bloom strength

Type of gelatin	Concentration (%, w/w)	Dipping temperature (°C)	Viscosity (cp) (60 °C)	Withdrawal time (s)
B 260 bloom	35	56 ± 3	205	5–12
B 80 bloom	35	40 ± 1	102	12–15
B 43 bloom	35	40 ± 1	82	12–15

(Table 2). The shell thickness of the capsules was determined by pressing the body part of the capsule together on a flat surface. The shell thickness (half of the measured value) was then measured with a thickness gauge Minitest 600 (Erichsen, Hemer, Germany).

2.6. Mechanical properties of capsules

The hardness of the capsule shells was determined by two different methods:

(a) *Puncture test*: A metal probe (diameter 5 mm, length 15 cm) was driven at a speed of 5 mm/min onto the cap of vertically fixed capsule. The force acting on the probe was recorded with an Instron® Testing Machine 4466 (Wolpert GmbH, Darmstadt, Germany) equipped with a 500 N load cell. The hardness of the capsule was the force to break the capsule ($n = 6$).
(b) *Shionogi test* (Shionogi, 1998): The brittleness of the capsules was determined by dropping a 50 g weight from a distance of 10 cm onto 20 capsules. The percentage of broken capsules was taken as percentage brittleness. The capsules were stored at different relative humidity conditions. The highest humidity condition for gelatin capsules was 68% RH and for HPMC capsules 75% RH.

2.7. Disintegration times of films and capsules

The in vitro disintegration time of films and capsules was measured in pH 6.8 phosphate buffer at 37 °C using a disintegration tester (Erweka, ZT3). The in vivo disintegration time (time, at which the capsule disintegrated/partly dissolved and released its content) in the oral cavity and the palatability of the capsules were determined in four volunteers.

The capsules were filled with a hand-operated capsule-filling machine.

2.8. Moisture content of the capsules

Twenty capsules were stored in a dessicator over silicagel for 3 days. The capsules were weighed and stored for 3 days in desiccators containing silicagel (0%) or saturated salt solutions to give humidity values of 27% (potassium acetate), 44–51% (potassium carbonate), 68% (sodium nitrate) and 75% (amonium chloride) at room temperature. The capsules were than placed in oven at 105 °C and equilibrated. The moisture content of capsules was determined gravimetrically by reweighing the capsules after drying (loss on drying).

3. Results and discussion

The goal of this study was to prepare hard capsules (Fastcaps) with good processability (sufficient mechanical properties) and a rapid disintegration in the saliva. The Fastcaps were prepared by dipping process, which is also used to prepare conventional hard gelatin capsules. Prior to the preparation of the capsules, cast films were prepared from various gelatin solution formulations and evaluated with respect to disintegration and mechanical properties in order to identify suitable formulations for the capsule preparation.

3.1. Gelatin films

An adequate mechanical strength is required for the Fastcaps in order to withstand mechanical stress (e.g., filling and packaging processes, pushing through blister package, handling by patient). Conventional hard gelatin capsules are usually prepared from gelatin of high bloom strength (235–260) (Jones, 1987).

The mechanical properties of films prepared from gelatin of different bloom strength were determined by a puncture test. Puncture strength is a measure of film toughness and is directly proportional to the resis-

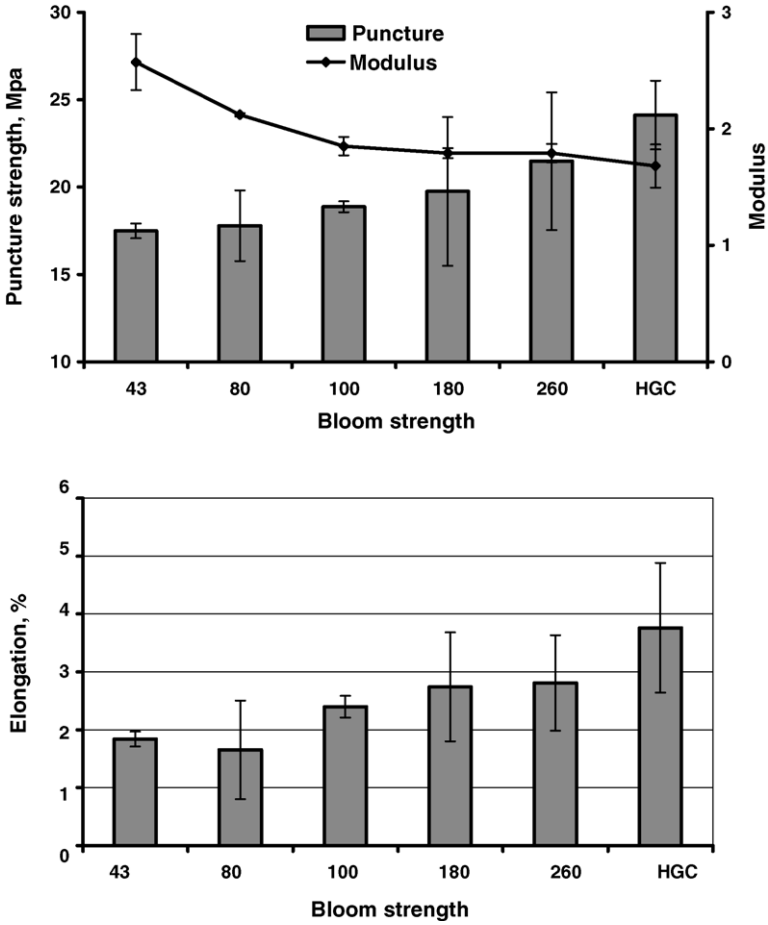

Fig. 1. Mechanical properties (puncture strength, elastic modulus and elongation) of gelatin films made from gelatin of different bloom strength and of commercial hard gelatin capsules (HGC).

tance to break or fracture. The puncture strength and elongation increased and the modulus decreased with increasing bloom strength (Fig. 1). Films prepared from dissolved conventional hard gelatin capsules (HGC) and from gelatin of 260 bloom strength had the highest puncture strengths, while films from gelatin of 43 bloom strength had the lowest. Similarly, HGC films and films from gelatin of 260 bloom required the greatest energy to puncture, while films from gelatin of 43 bloom required the lowest (data not shown). Therefore, films from gelatin of low bloom strength had the lowest least resistance to breakage.

The thickness of the films (capsule shells) is an important parameter affecting the disintegration time. Conventional hard gelatin capsules have a thickness of approximately 100 μm, which was also selected as the thickness of the Fastcaps. A reproducible film thickness was achieved by keeping the solid content in the gelatin solutions constant.

As expected, the disintegration time of films decreased with decreasing bloom strength (Fig. 2). Films prepared from gelatin of high bloom strength (180 or 260) required more than 5 min for disintegration, while gelatin films prepared from the low bloom strength (43) disintegrated in less than 1 min. A further decrease in the disintegration time was obtained by the addition of xylitol (10 and 15%, w/w), which also improved the mechanical properties of films from gelatin of low bloom strength (data shown in next section).

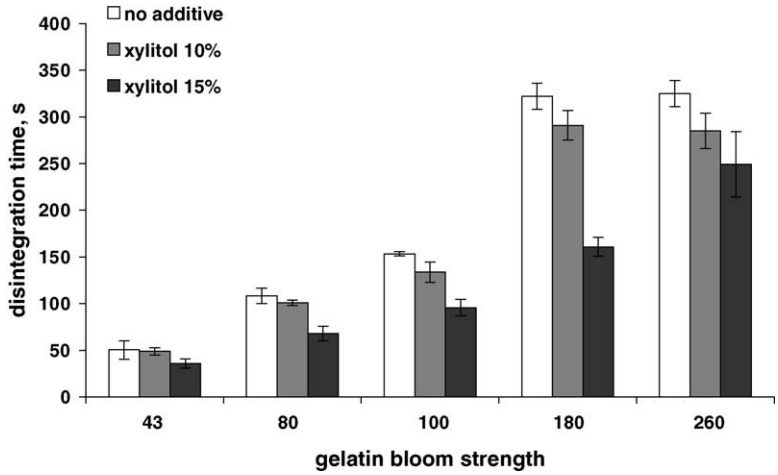

Fig. 2. Effect of bloom strength and of xylitol on the disintegration time of gelatin films.

PEG 4000 had almost no influence on the disintegration time, while PEG 400 or 1500, sorbitol and xylitol decreased the disintegration time. These hydrophilic additives increase the rate of dissolution of gelatin films, which is desirable (Fig. 3).

Increasing amounts of xylitol only slightly affected the puncture strength, but resulted in an increase in elongation and thus in a decrease of the modulus (Fig. 4). Xylitol is hygroscopic**,** resulting in more water retained in the films and thus more flexible films. This may require longer drying times and difficulties at the trimming stage during capsule production. The addition of PEGs gave similar effects as xylitol. However, PEG 1500 and 4000 resulted in turbid films at concentration above 5% (w/w), indicating the immiscibility of the solid PEGs with gelatin. Films with more than 5% (w/w) PEG 400 resulted in elastic, sticky and difficult to process films.

3.2. Fast disintegrating gelatin capsules (Fastcaps)

Based on the screening studies with additive-containing low bloom strength gelatin films, fast disintegrating capsules were prepared. The following parameters were important for the preparation of

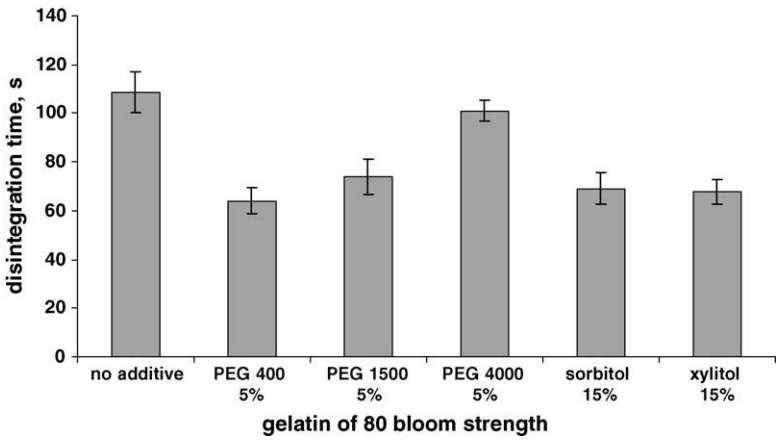

Fig. 3. Effect of different additives on the disintegration time of gelatin films (80 bloom strength).

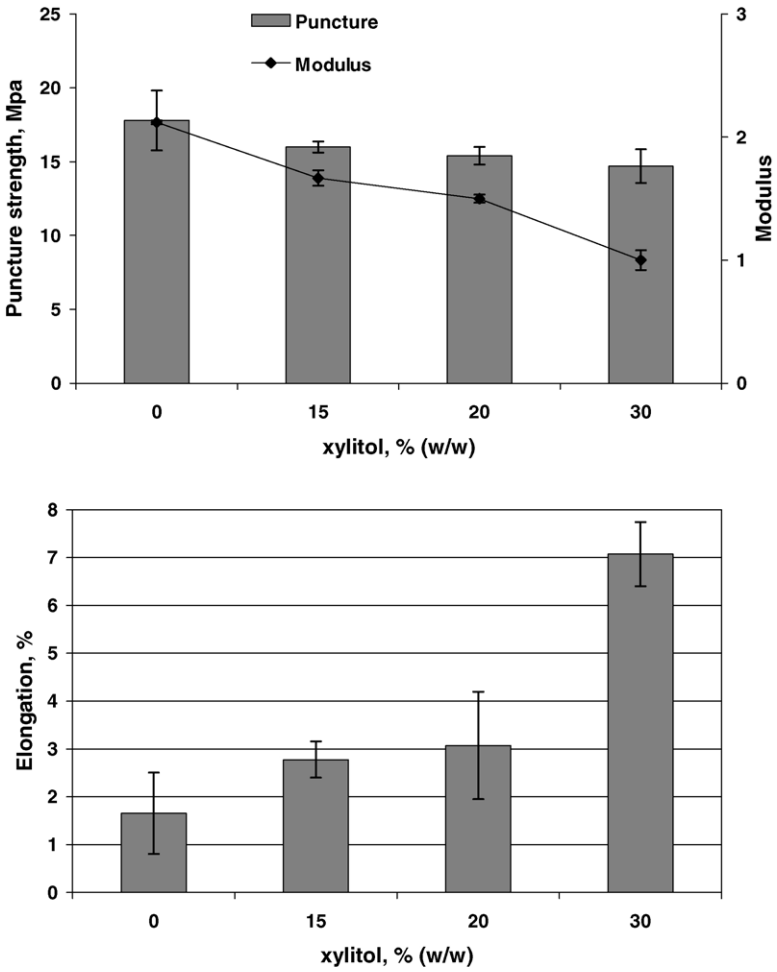

Fig. 4. Effect of xylitol concentration on the mechanical properties (puncture strength, elastic modulus and elongation) of gelatin films (bloom strength 80).

Fastcaps by the dipping method: (1) the viscosity of the gelatin solution; (2) the temperature of the gelatin solution (dipping temperature); (3) the velocity, at which the steel pins were withdrawn from the dipping solution. The latter parameter significantly affected the thickness and homogeneity of the capsule shell. Each gelatin type (different bloom strength) required different preparation conditions (Table 2). Gelatin of 260 bloom strength, which is used for the preparation of conventional hard gelatin capsules, was included in the study for comparative studies with the Fastcaps. The necessity of different preparation conditions for different gelatins can be attributed to the different viscosities of the dipping solutions.

The viscosity and sol–gel transition temperature of the dipping solution affected the amount and the distribution of the gelatin solution around the dipping steel pins. At the same temperature (60 °C), the viscosity of the gelatin solution decreased with decreasing bloom strength/molecular weight (Fig. 5). The lower solution viscosity of the lower bloom strength gelatin solutions would result in an insufficient amount of gelatin solution adhering to the pins. The lower viscosity was compensated by a lowering of the dipping temperature (thus increasing the solution viscosity) and by increasing the dipping time, which assured a homogeneous distribution of the gelatin solution around the pin. The required viscosity range for Fastcap manufacturing was approx-

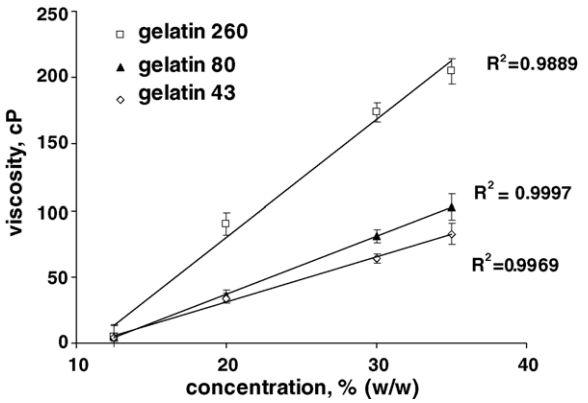

Fig. 5. Effect of gelatin solution concentration and bloom strength on the viscosity of gelatin solutions at 60 °C.

imately 500–600 cP (Fig. 6). Interestingly, the addition of the hydrophilic additives (15% xylitol or sorbitol or 5% PEG 1500) did not significantly affect the viscosity of gelatin solution (data not shown). The preparation conditions therefore did not require adjustments for the additive-containing dipping solutions. Sorbitol led to difficulties during stripping the hardened capsule shells from the steel pins, whereas PEG 1500 facilitated this processing step because of its lubrication effect.

Besides the viscosity of the dipping solution, its sol–gel transition temperature is important for the dipping process. The sol–gel transition temperature was determined as the cross point of the two extrapolated lines of the viscosity–temperature curve. The sol–gel transition temperature for aqueous solutions of gelatin of 260, 80 and 43 bloom strength were approximately

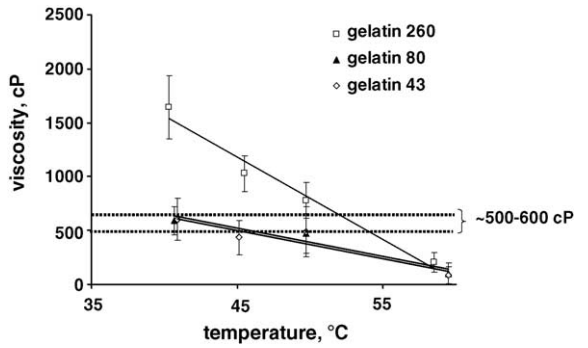

Fig. 6. Effect of temperature and bloom strength on the viscosity of 35% (w/w) gelatin solutions the required viscosity range for Fastcap manufacturing.

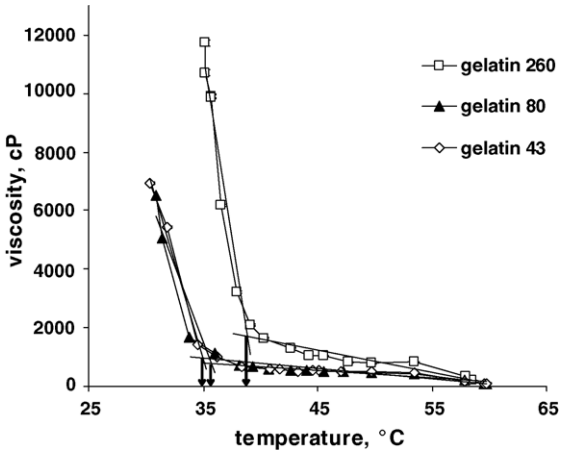

Fig. 7. Temperature dependent sol–gel transition of aqueous 35% (w/w) gelatin solutions (bloom strength 260, 80, 43).

38, 35.5 and 35 °C, and thus were quite similar (Fig. 7). The addition of xylitol (5, 15 and 20%, w/w) did not change the gelation temperature of gelatin 80 (data not shown).

In summary, the laboratory-scale manufacturing process of the Fastcaps was well controlled and reproducible as shown by the very similar dimensional specifications and moisture content of the Fastcaps, when compared to commercial (Shionogi) capsules (Table 3).

3.2.1. In vitro and in vivo disintegration time of Fastcaps

The in vitro disintegration of the Fastcaps (approximately 30–45 s) was about twice as rapid as the one of regular hard gelatin capsules (HGC) (approximately 70 s) (Table 4). The in vivo mouth performance and disintegration was investigated with four volunteers. Conventional hard gelatin capsules disintegrated slower (30 s) and resulted in a sticky feeling and formed a highly viscous gel in the mouth. In contrast, Fastcaps rapidly disintegrated (9–13 s) and their content was rapidly spread throughout the oral cavity within seconds. In addition, xylitol resulted in a pleasant taste of the capsules and produced a cooling effect in the mouth as a result of its negative heat of solution. It also has the unique property of being anticariogenic. The in vivo disintegration time in the mouth was much shorter when compared to the in vitro disintegration time, probably because of the movement of the capsule in the mouth and hence gentle mechanical stress on the

Table 3
Dimensional specifications and residual moisture contents of gelatin capsules ($n = 6$)

Capsules (size #1)	Capsule weight (mg)		Capsule length (mm)	Shell thickness (μm)	Moisture content (%, w/w)
	Body	Cap			
Shionogi capsules	47.2 ± 0.3	18.7 ± 0.2	28.3 ± 0.1	108 ± 3	15.1 ± 0.2
Fastcap, 15% sorbitol	48.2 ± 0.9	19.1 ± 0.3	29.3 ± 0.3	111 ± 9	12.1 ± 0.2
Fastcap, 15% xylitol	46.2 ± 0.5	18.8 ± 0.3	27.6 ± 0.3	106 ± 5	11.8 ± 0.1
Fastcap, 5% PEG 1500	46.6 ± 0.5	18.7 ± 0.2	27.9 ± 0.3	107 ± 7	14.2 ± 0.2

capsules. The use of lower bloom strength gelatin and hydrophilic additives (xylitol or PEG) additives therefore significantly improved the disintegration time and also the palatability of the capsules.

Besides the capsule shell, the capsule content could also influence the performance of the capsules. Capsules were therefore filled with water-soluble fillers (lactose, saccharose and glucose) and/or disintegrants (microcrystalline cellulose/Avicel® PH101, crosslinked sodium carboxymethylcellulose/Ac-di-sol® or sodium starch glycolate/Explotab®). The disintegration times of conventional HGC containing the water-soluble fillers (62, 73 and 75 s for lactose, saccharose and glucose, respectively) were not significantly different from those containing disintegrants (69, 75 and 84 s for microcrystalline cellulose, crosslinked sodium carboxymethylcellulose or sodium starch glycolate, respectively) (data not shown). Fastcaps prepared from gelatin of 43 and 80 bloom strength containing lactose or microcrystalline cellulose disintegrate in half the time (approximately 28–36 s) than filled conventional hard capsules. Lactose and/or Avicel® PH101 are therefore suitable excipients for the filling of Fastcaps.

Table 4
In vitro and in vivo disintegration times of conventional hard gelatin capsules and Fastcaps (in vitro, empty capsules; in vivo, capsules filled with lactose)

Capsules	Disintegration time (s)	
	In vitro	In vivo
Shionogi capsules	69 ± 3	30 ± 9
Shionogi PEG capsules	71 ± 4	30 ± 7
Fastcap 43, 15% xylitol	31 ± 3	9 ± 3
Fastcap 80, 15% xylitol	41 ± 4	11 ± 3
Fastcap 80, 5% PEG 1500	44 ± 6	13 ± 4

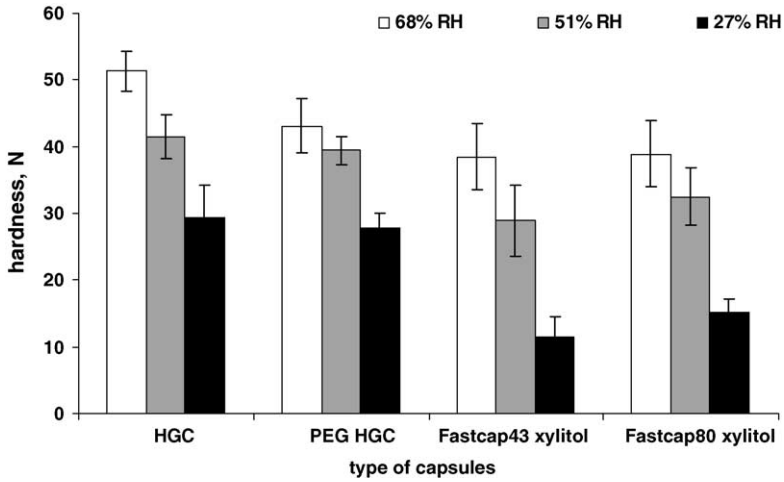

Fig. 8. Hardness of conventional hard gelatin capsules (HGC and PEG HGC) and Fastcaps after storage at various humidity levels (determined with puncture test).

3.2.2. Mechanical strength

The mechanical strength of Fastcaps was compared to commercially available hard gelatin capsule (Shionogi capsules with and without PEG) (Fig. 8). All capsules were stored at three different relative humidities (27, 51, 68% RH) for one week. The hardness values, as determined with an Instron, were in the order of HGC > PEG HGC > Fastcaps 80 = Fastcap 43. However, the hardness of the new type of fast-dissolving gelatin capsules was not much different when compared to the hardness of conventional gelatin capsules (of high bloom strength). Only at a low 27 RH, the Fastcaps were significantly more brittle. As expected, the hardness decreased with all capsules with increasing storage humidity because of the plasticizing effect of water.

The mechanical properties depend strongly on the moisture content of the capsules. The lower moisture content, the more brittle the capsule shells become and they could therefore potentially break during processing and handling. A relationship between brittleness and moisture content was determined with the Shionogi test. The percentage of broken gelatin capsules (brittleness) sharply increased when the moisture content of HGC, PEG-HGC and Fastcaps dropped below 10% (w/w) (Fig. 9). No significant differences were seen between Fastcaps and conventional capsules. In contrast, HPMC capsule shells were not brittle, even at a low moisture level of only 2%. However, HPMC capsules to not dissolve rapidly in the mouth. In summary, Fastcaps had similar mechanical properties as commercially available gelatin capsules.

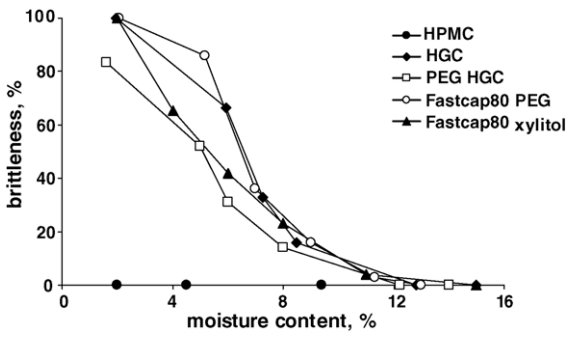

Fig. 9. Mechanical properties of conventional hard capsules (HGC, PEG HGC and HPMC capsules) and Fastcaps at various moisture contents (Shionogi brittleness test).

References

Bodmeier R., 1999. Darreichungsform zur Applikation in Körperöffnungen. German Patent Application DE 19922537.

Bodmeier, R., Paeratakul, O., 1993. Dry and wet strengths of polymeric films prepared from an aqueous colloidal polymer dispersion, Eudragit RS30D. Int. J. Pharm. 96, 129–138.

Charman, S.A., Charman, W.N., 2002. Oral modified-release delivery systems. In: Rathbone, Hadgraft, Roberts (Eds.), Modified-Release Drug Delivery Technology. Marcel Dekker Inc., pp. 1–10.

Cherukuri S.R., 1996. Process for forming quickly dispersing comestible unit and product there from. US Patent 5,587, 172.

Clarke, A., Johnson, E.S., Mallard, N., Corn, T.H., Johnston, A., Boyce, M., Warrington, S., MacMahon, D.G., 2003. A new low-dose formulation of selegiline: clinical efficacy, patient preference and selectivity for MAO-B inhibition. J. Neural Transm. 110, 1257–1271.

Corveleyn, S., Remon, J.P., 1997. Formulation and production of rapidly disintegrating tablets by lyophilisation using hydrochlorothiazide as a model drug. Int. J. Pharm. 152, 215–225.

Fix, J.A., 1998. Advances in quick-dissolving tablets technology employing Wowtab. In: Institute for Int. Resources, Conference on Drug Delivery Systems, October, Washington DC, USA.

Habib, W., Khankari, R., Hontz, J., 2000. Fast-dissolve drug delivery systems. Crit. Rev. Ther. Drug Carrier Syst. 17, 61–72.

Jones, R.T., 1987. Hard Capsules. Development and Technology. K. Ridgway Chap. Pharmaceutical Press, London.

Kearney, P., 2002. The Zydis oral fast-dissolving dosage form. In: Rathbone, Hadgraft, Roberts (Eds.), Modified-Release Drug Delivery Technology. Marcel Dekker Inc., pp. 191–201.

Pather, S.I., Khankari, R.K., Moe, D.V., 2003. OraSolv and Dura-Solv: efficient technologies for the production of orally disintegrating tablets. In: Rathbone, Hadgraft, Roberts (Eds.), Modified-Release Drug Delivery Technology. Marcel Dekker Inc., pp. 203–216.

Radebaugh, G.W., Murtha, J.L., Julian, T.N., Bondi, J.N., 1988. Methods for evaluating the puncture and shear properties of pharmaceutical polymeric films. Int. J. Pharm. 45, 39–46.

Sastry, S.V., 2000. Recent technological advances in oral drug delivery—a review. Pharm. Sci. Technol. Today 3, 138–145.

Seager, H., 1998. Drug-delivery products and the Zydis fast-dissolving dosage form. J. Pharm. Pharmacol. 50, 375–382.

Shionogi Qualicaps Product Brochure, 1998. Gelatin/PEG capsules. SQ 005-1998E.

Smith T., Sharp J., Andreasen S., 2001. The Zydis® drug delivery system. Pharmaceutics III.

Virely, P., Yarwood, R., 1990. Zydis—a novel, fast dissolving dosage form. Manuf. Chem. February, 36–37.

Wilson, C.G., Washington, N., Peach, J., Murray, G.R., Kennerley, J., 1987. The behavior of a fast dissolving dosage form (Expidet) followed by γ-scintiagraphy. Int. J. Pharm. 40, 119–123.