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Research paper

Modified conventional hard gelatin capsules as fast disintegrating dosage form in the oral cavity

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Abstract

Fast disintegrating capsules for administration in the oral cavity were prepared either by perforation or by vacuum-drying of conventional hard capsules. When compared to other fast disintegrating dosage forms (e.g. lyophilized sponges or tablets), these capsules have various advantages, in particular, a high drug loading capacity and no compression steps. The disintegration time of conventional hard gelatin capsules (HGC) was reduced from 91 to 39 s by introducing 6–10 small holes (diameter = 25–50 μm) into the capsule shell. Vacuum-drying of conventional hard gelatin capsules resulted in brittle capsules, which broke rapidly in the oral cavity. The brittleness of the hard gelatin capsules correlated well with their moisture content. The critical moisture value for sufficient brittleness of hard gelatin capsules was $<4\%$ w/w. In contrast, HPMC capsules remained flexible, even at low moisture content. The moisture uptake of various capsule fillers was in the order of Avicel® PH101 > lactose > Avicel® PH112 ≥ mannitol. Hard gelatin capsules filled with mannitol and packaged in bottles with silica gel kept their desired brittleness during 6 months storage at various relative humidities.
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Keywords: Capsules; Fast disintegrating dosage forms; Oral cavity

1. Introduction

Fast disintegrating/dissolving dosage forms for the oral cavity are preferred by an increasing number of patients, especially children and elderly people. In addition, adult consumers often like to have their medication readily available at any time (e.g. without water) [1]. Patients appreciate the convenience of these dosage forms, which can be taken without water, which are easily swallowed, and which often have a quick onset of action [2].

Several technologies for orally disintegrating dosage forms, such as lyophilized formulations, fast-dissolving tablets and oral films have been developed. The Zydis™ dosage form, developed by Scherer, is the fastest dissolving system available and dissolves within a few seconds in the oral cavity [3,4]. This dosage form is produced by freeze-drying aqueous drug/excipient suspension/solutions within blister packs [5]. The final product is a dried, sponge-like tablet in a special peel-off blister pack. Major disadvantages of the Zydis® technology is the time-consuming freeze-drying process, the limitation to low dose drugs, the poor mechanical properties and the 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 [6]. The Shearform™ technology is based on tablets prepared by compression of cotton candy-like fibers [7,8]. The resulting tablets are soft, friable, and highly moisture-sensitive [9]. Fast disintegrating intraoral films differ from the other types of fast disintegrating dosage forms with regard to shape/appearance and manufacturing process. The water-soluble films are moisture-sensitive; in addition, their drug loading capacity is probably the lowest among all fast disintegrating dosage forms.

The main disadvantages of fast-disintegrating systems such as low drug loading, time-/cost-consuming manufacturing and insufficient taste masking can be overcome with a new delivery system investigated in this study. The objective of this work was to prepare fast disintegrating capsules for the oral cavity from conventional hard capsules by perforation or vacuum-drying.

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2. Materials and methods

2.1. Materials

Hard gelatin capsules (size 1) and hydroxypropyl methylcellulose capsules (HPMC, size 1) (Shionogi Qualicaps Co., Ltd, Nara, Japan), microcrystalline cellulose (Avicel® type PH101 and type PH112, FMC Co., Brussels, Belgium), hydroxypropyl methylcellulose, mannitol (Roquette Frères Co., Lestrem, France), lactose (D(+)-lactose monohydrate, Riedel-de Haën AG, Seelze Germany), saccharose (Merck KGaA, Darmstadt, Germany), maize starch (Roquette Frères Co., Lestrem, France).

2.2. Preparation of perforated capsules

Conventional hard capsules, empty or filled with different fillers (250–350 mg, lactose, saccharose, Avicel® PH101 or maize starch) were perforated with a needle (2, 6, 10 holes) at the top or along the longitudinal section to reduce the disintegration time of the capsules. The size of the holes was approximately 25–50 μm.

2.2.1. Mechanical properties of the perforated capsules

The brittleness of conventional and perforated capsules was determined with the Shionogi test [10] by dropping a 50 g weight from a distance of 10 cm onto the capsules (20 capsules). The percentage of broken capsules was taken as the percent brittleness.

2.3. Preparation of vacuum-dried, brittle capsules

Twenty capsules (hard gelatin capsules and HPMC) were accurately weighed (Mettler AT250, Mettler-Toledo GmbH, Ockerweg, Germany) and equilibrated in a desiccator over a saturated salt (potassium carbonate) solution (giving a 51% relative humidity) for 3 d. These capsules (empty or filled) were then dried in a vacuum-oven (Heraeus VT 5042 EKP, Hanau, Germany) at 30 and 40 °C. The weight loss of the capsules during drying was determined gravimetrically at predetermined time points.

2.3.1. Moisture content of the capsules

Twenty capsules were equilibrated in a desiccator over silicagel for 3 d. The capsules were accurately weighed and then stored for 3 d in desiccators containing saturated salt solutions to give storage relative humidities of 27% (potassium acetate), 51% (potassium carbonate), 68% (sodium nitrate) and 75% (ammonium chloride) at room temperature. The moisture content of capsules was determined gravimetrically by reweighing the capsules after drying in an oven at 105 °C, until no further weight loss was obtained (loss on drying, LOD) .

The equilibrium moisture content of the fillers (Avicel® PH 101, Avicel® PH 112, lactose and mannitol) was determined similarly.

2.3.2. Brittleness of the capsules

The brittleness of the capsules was related to their moisture content. Capsules (empty or filled) with various moisture contents were put on a flat surface. A force was uniformly applied with a finger onto the capsule. The application of the force with a finger could simulate forces applied in the oral cavity (e.g. by the tongue). The capsules were then ranked qualitatively for brittleness as follows: highly brittle capsule: breakage into small pieces; brittle capsule: cracked and/or broken into two pieces; flexible capsule: deformed under force without breakage or splitting. The critical moisture content for the capsules was the moisture content, at which the capsule broke into small pieces.

2.3.3. Storage of the capsules

Immediately after vacuum-drying, the capsules (empty or filled) were placed either into tightly closed glass vials containing silica gel or plastic bottles with/without silica gel. The containers were stored in desiccators at room temperature at 0, 51 and 75% relative humidity for 6 months. Samples were evaluated for their moisture uptake at predetermined time points.

2.4. Disintegration time

The in vitro disintegration time of perforated capsules was determined in 0.1 M pH 6.8 phosphate buffer at 37 °C in a disintegration tester (Erweka ZT3) ($n=3$). The disintegration time was defined as the time necessary for complete opening of the capsules and release of the fillers.

The in vivo disintegration time of conventional, perforated and vacuum-dried capsules was determined in four healthy volunteers and was the time necessary for rupturing/breaking of the capsules and release of their content in the oral cavity.

3. Results and discussion

Fast disintegrating capsules for application in the oral cavity were prepared by modification of conventional hard gelatin capsules. Two approaches were investigated. The capsules were either perforated with small holes to promote rapid ingress of aqueous fluids and therefore a faster disintegration, or the moisture content of the capsules was reduced by vacuum-drying resulting in brittle capsules. The brittle capsules easily break upon the exertion of low mechanical forces within the oral cavity (e.g. tongue movement).

These modified capsules for use in the oral cavity have various advantages compared to other fast disintegrating dosage forms, including a high drug loading capacity, no need for large quantities of excipients, no compression step (no damage of coated taste-masked or modified release particles) and improved drug stability (only solid drug processed vs. drug solution/suspensions in the case of Zydis and films) (Table 1).

3.1. Perforated hard gelatin capsules

Conventional hard gelatin capsules were perforated with 2, 6 or 10 holes at the top or along the longitudinal side in order to

Table 1
Comparison of perforated or vacuum-dried, brittle capsules vs. other fast disintegrating dosage forms for the oral cavity

Parameter	Capsules	Zydis®	Tablets	Films
Rate of disintegration[a]	3	1	4	2
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[b]	No/yes	No	No	No
Special packaging[b]	No/yes	Yes	?	Yes

[a] 1, Fastest, 4 longest disintegration.
[b] Yes for vacuum-dried, no for perforated capsules.

reduce the disintegration time of the capsules. The holes had a diameter between 25 and 50 μm and were made on a lab-scale with a needle. On a production scale, other methods to the form the holes have to be used, for example, the use of a laser technology similar to the preparation of holes in the coating of osmotic tablets, whereby a cellulose ester coating is perforated with a laser beam.

Perforated capsules disintegrated significantly faster than conventional non-perforated capsules (Table 2). The disintegration time was more than halved with capsules having 10 holes (92 vs. 39 s for conventional capsules). The disintegration medium penetrated into the capsules through the holes and started to dissolve/weaken the capsule shell from both the in- and outside. The locations of the holes at either the top or along the longitudinal side of the capsules did not affect the disintegration time.

The holes have to be small enough to prevent loss of the powder/granule filling during manufacture, storage or administration. Therefore, excipients with a proper particle size or granules/pellets have to be selected or to be prescreened to remove smaller particles. Capsule fillers chosen for this study were either water-soluble (lactose or saccharose) or water-insoluble/swelling (microcrystalline cellulose/Avicel® PH101 or corn starch). Avicel® PH101 resulted in the fastest disintegration time, probably because of its rapid water absorption and swelling (Table 3).

The in vivo disintegration of the perforated capsules was investigated in four healthy volunteers (Table 4). Conventional hard gelatin capsules were very sticky, disintegrated slowly and formed a highly viscous paste in the mouth. In contrast, the perforated capsules disintegrated quickly and their content was rapidly spread throughout the oral cavity. The in vivo disintegration time was much shorter than the in vitro disintegration time, probably because of the movement of the capsule in the mouth and hence gentle mechanical stress on the capsules.

Table 2
The effect of number of holes and location on the in vitro disintegration time of empty/filled (Avicel® PH101) hard gelatin capsules

Holes		Disintegration time of capsules (s)	
Number	Position	Empty	Filled with Avicel® PH101
–	–	91.2±4.5	91.2±4.5
2	Top	74.4±9.8	73.6±10.8
6	Top	46.6±7.8	48.4±9.2
10	Top	38.6±3.9	47.2±4.9
2	Longitudinal	73.6±10.9	71.6±8.4
6	Longitudinal	50.6±3.9	49.0±5.9
10	Longitudinal	40.2±5.3	44.4±5.7

Table 3
The effect of different fillers on the in vitro disintegration time of hard gelatin capsules (10 holes at the top of the capsules)

Filler	Disintegration time (s)
Avicel® PH101	44.4±5.7
Lactose	71.9±4.0
Starch	73.8±4.4
Saccharose	81.9±5.0

The mechanical properties of the capsule shells are important in order to resist damage during large-scale filling and packaging of the capsules. Conventional and perforated hard gelatin capsules showed a similar resistance towards breakage at the same moisture content of the capsules, as determined by the Shionogi test (Fig. 1). The breakage of the capsules only slightly increased with increasing number of holes. Thus, perforated hard gelatin capsules would run on automated capsule filling and packaging machines.

3.2. Vacuum-dried, brittle capsules

Another approach to improve the disintegration of conventional hard capsules was obtained by vacuum-drying the capsules. Hard gelatin capsule shells usually contain between 13 and 16% w/w moisture [11]. A decreasing relative humidity (at constant temperature) or an increasing temperature (at constant relative humidity) leads to a moisture loss (desorption) and more brittle capsule shells. Special packaging for capsules is often needed to avoid moisture transfer from the environment [12].

In this study, the hard capsules were dried to a much lower moisture contents. The vacuum-drying resulted in mechanically weak, brittle capsules because of the low moisture content of the capsules. The brittle capsules thus broke easily in the mouth and released their content very quickly. These capsules would require special packaging because of their weak mechanical properties and moisture sensitivity. Special blister packaging, whereby the dosage form is not pushed through the

Table 4
In vivo disintegration time of perforated (top positioned holes) and vacuum-dried hard gelatin capsules

Capsules	Disintegration time (s)
Conventional	30.8±4.5
Perforated	
2 Holes	26.8±9.8
6 Holes	17.0±7.8
10 Holes	12.5±3.9
Vacuum-dried	7.1±4.8

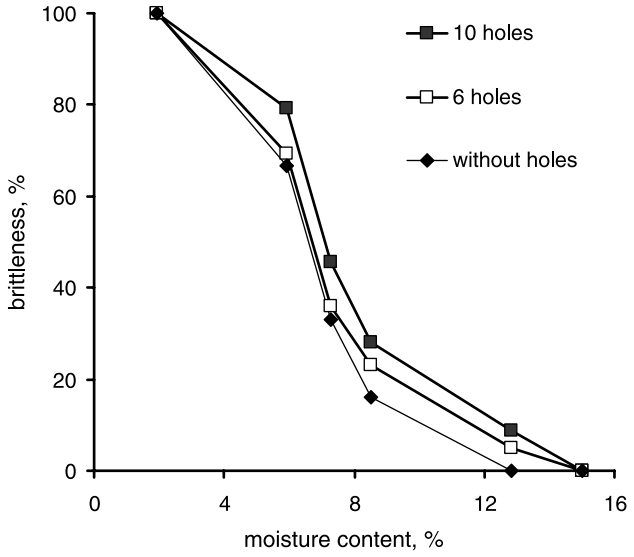

Fig. 1. Brittleness of conventional hard gelatin capsules and capsules with 6 or 10 holes.

blister but removed by pulling off a sealing foil, could be used. This technology is already used for freeze-dried or soft tablets [1].

Vacuum-drying allows the drying of the capsules at lower temperatures and in shorter times. Commercially available hard gelatin and HPMC capsules were investigated for the potential to form brittle capsules upon drying. The initial moisture content of hard gelatin capsules was higher than the one of HPMC capsules (15 vs. 5%). The moisture content decreased sharply for both capsule types during the first 3 h of vacuum-drying at 30 and 40 °C (Fig. 2). The minimum moisture content under these drying conditions was 0.3% w/w for HPMC capsules and 0.6% for hard gelatin capsules.

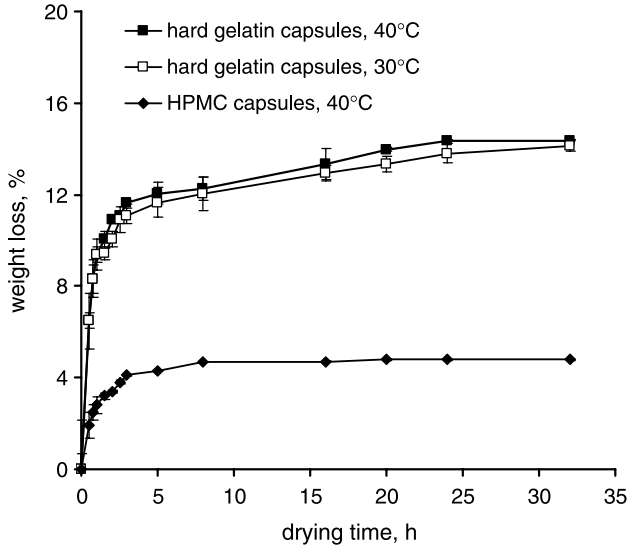

Fig. 2. Weight loss of empty hard gelatin and HPMC capsules as a function of vacuum-drying time at 30 and 40 °C.

Another important parameter affecting the moisture content of the capsule shell and hence its brittleness is the capsule content, which represents the major weight part of a filled capsule (weight of capsule shell = 85–95 mg, filling weight = 250–350). The moisture content of fillers is critical because of potential migration of moisture from the fillers into the shell during storage. Two grades of microcrystalline cellulose, Avicel® PH101 and the low moisture grade Avicel® PH112, and lactose and mannitol were evaluated. The equilibrium moisture content of the fillers was in the order of Avicel® PH101 (6.31%) > lactose (4.24%) > Avicel® PH 112 (0.31%) ≥ mannitol (0.29%) (Fig. 3). Therefore, Avicel® PH 112 and mannitol were the most suitable fillers for vacuum-dried hard gelatin capsules.

The weight loss of hard gelatin capsules filled with different fillers (350 ± 10 mg) during vacuum-drying is shown in Fig. 4. The total starting moisture content of the filled capsules was lower than of the empty capsule shells because of the lower moisture content of the fillers. As with empty capsule shells (Fig. 2), a low moisture content of 3.3 (at 40 °C) or 3.9% (at 30 °C) was obtained quickly after a drying time of only 1.5–3 h. A moderate drying temperature of only 30 °C was, therefore, sufficient for the preparation of brittle capsules.

Next, a relationship between the moisture content of the capsule shell and its brittleness was established (Table 5). In order to release the content rapidly, the capsules have to be brittle enough to break in the oral cavity through the application of a force, for example by tongue movement. Hard gelatin capsules became brittle at a moisture content of between 5.6 and 3.9% w/w (after 1 and 2.5 h vacuum-drying). A further decrease in moisture content to < 3.9% w/w (3 h vacuum-drying) resulted in highly brittle capsule shells; all capsules broke into small pieces. A critical moisture content of approx. 4% or less was, therefore, desirable in order to obtain rapidly and completely breaking hard gelatin capsules. HPMC capsules did not break, but only deformed even at the lowest moisture content. HPMC is a much more flexible

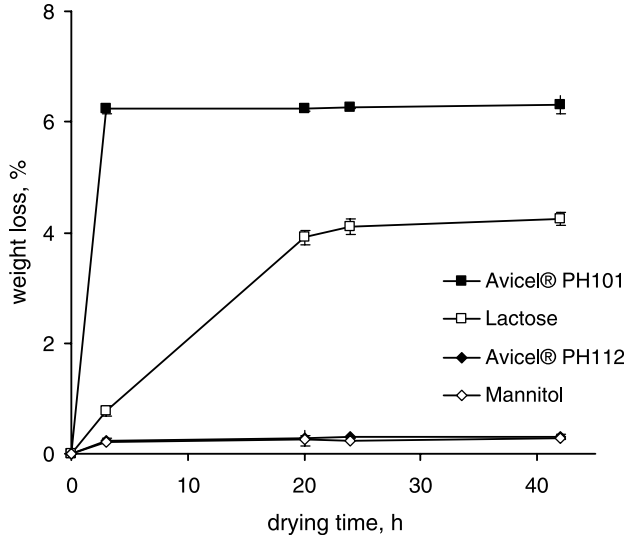

Fig. 3. Weight loss of different fillers as function of drying time at 105 °C.

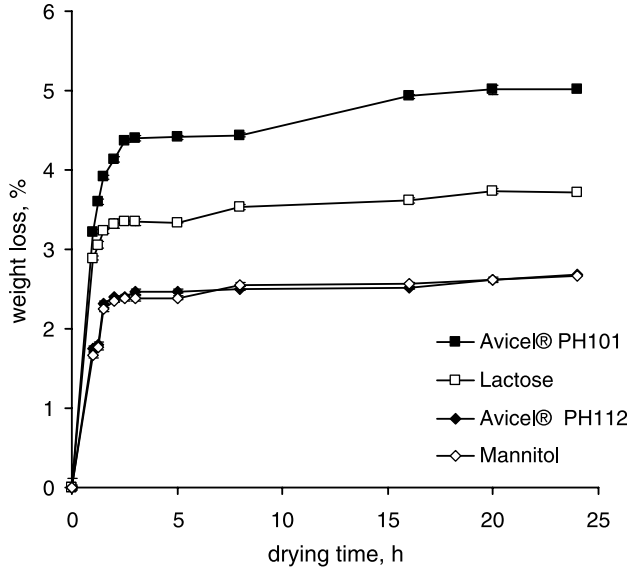

Fig. 4. Weight loss of hard gelatin capsules filled with different fillers as a function of vacuum-drying time at 40 °C.

polymer than gelatin. Thus, HPMC capsules were not suitable for use as brittle capsules in the oral cavity.

The breakage of the capsules will also be affected by the type of filler and its filling weight. Not completely filled capsules would give less resistance to breakage in the oral cavity than fully filled capsules. The moisture content—brittleness relationship was investigated for capsules filled with the various fillers (Table 5). The critical moisture value for Avicel® PH112-, mannitol-, lactose-, or Avicel® PH101-filled capsules to be highly brittle was <0.6, 0.6, 0.8 and 0.9%, respectively.

The in vivo disintegration time of the brittle capsules was reduced from 30.8 s for conventional capsules to 7.1 s (Table 4). Conventional hard gelatin capsules had a mechanically flexible shell, resulting in delayed disintegration/dissolution and formation of a highly viscous paste in the oral cavity. Thus, a fast disintegration was obtained with a low mechanical force exerted in the oral cavity. The broken capsule parts hydrated rapidly, were soft and not sharp, and resulted in a pleasant mouth feel.

Hard capsules are usually filled with solid materials [13], but some drugs were also filled as a liquid formulation for solubility

Table 5
Moisture content-brittleness (flexible, brittle, highly brittle capsules) relationship for capsules (empty or filled with various fillers)

Capsules	Filler	Moisture content (%)		
		Flexible	Brittle	Highly brittle
HPMC	Empty	5.0–0.2	–	–
Gelatin	Empty	>6.7	5.6–3.9	<3.9
Gelatin	Avicel® PH 101	>1.8	1.8–0.9	<0.9
Gelatin	Lactose	>1.1	1.1–0.8	<0.8
Gelatin	Avicel® PH 112	>0.8	0.8–0.6	<0.6
Gelatin	Mannitol	>0.7	0.7–0.6	<0.6

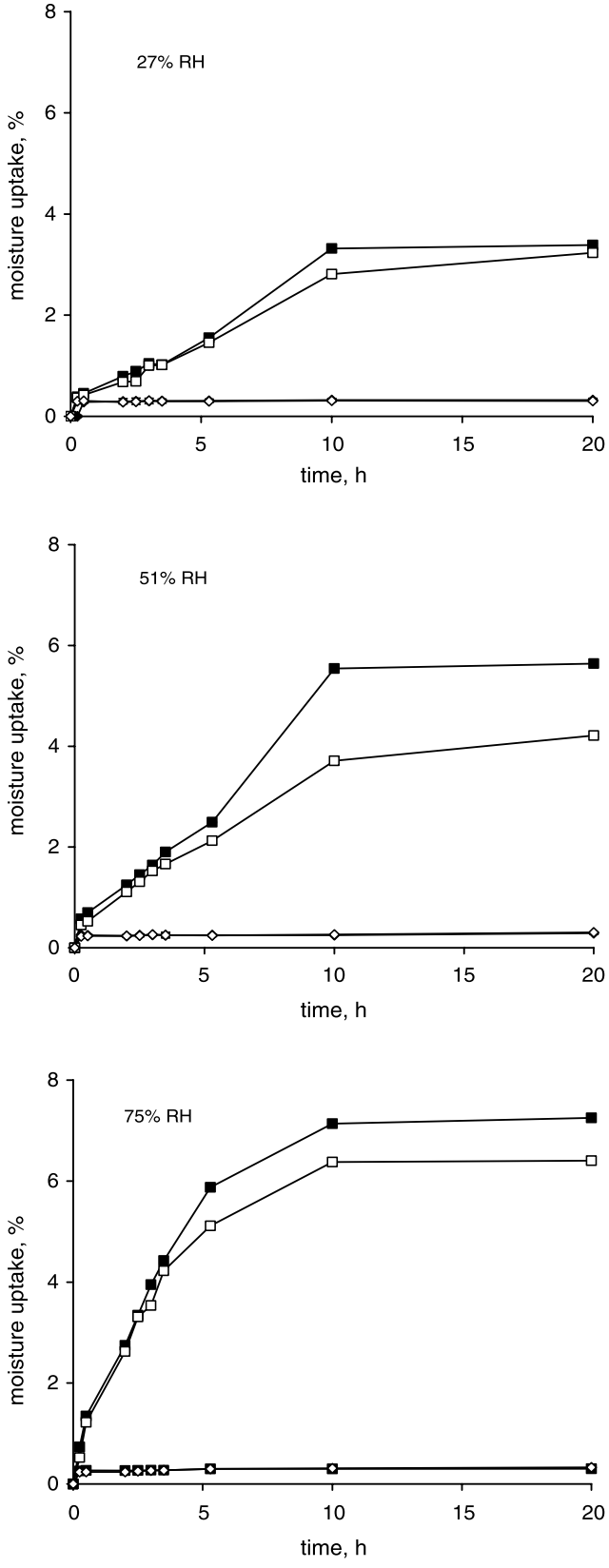

Fig. 5. Moisture uptake of different fillers during storage at different relative humidities: (■) Avicel® PH 101; (□) lactose; (♦) Avicel® PH112; (◊) mannitol.

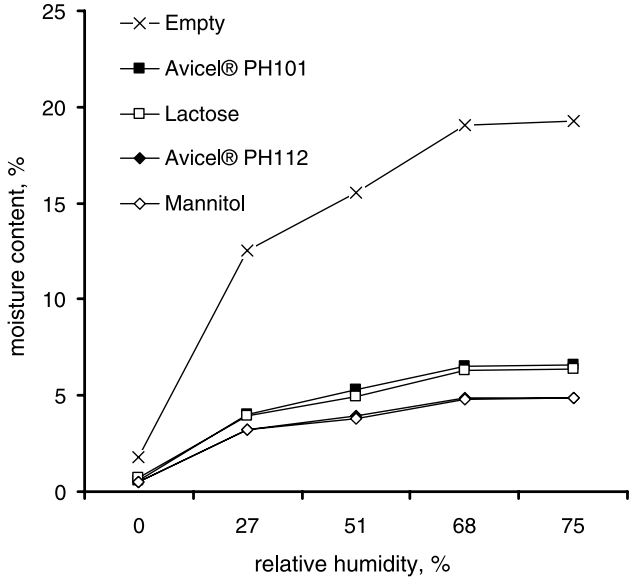

Fig. 6. Equilibrium moisture uptake of empty and filled hard gelatin capsules after storage at different relative humidities.

or bioavailability reasons [14]. Thus, non-volatile liquid or semisolid formulations, which do not plasticize the capsule shell, could potentially also be filled into the vacuum-dried capsules.

The moisture content of the capsule shell depends primarily on the type of fillers and the storage conditions (e.g. relative humidity). Because of the moisture-sensitivity of the vacuum-dried, brittle capsules, moisture uptake during storage has to be eliminated in order to maintain the brittleness necessary for rapid breakage/disintegration of the capsule. The filler should be non-hygroscopic and should have a low moisture content. The moisture uptake rate of the different fillers was determined at three storage humidities (27, 51, and 75% RH) (Fig. 5). The moisture uptake of Avicel® PH 101 increased continuously and reached its equilibrium value of approx. 3, 5, and 7% at 27, 51, and 75% RH after 10 h storage. Similarly, lactose took up approx. 3, 4, and 6% moisture. In contrast, the moisture uptake of Avicel® PH 112 and mannitol was less than 0.5%, irrespective of the storage humidity.

The moisture uptake of unpackaged, vacuum-dried hard gelatin capsules (empty and filled) was studied to determine their sensitivity to various humidity conditions (Fig. 6). As discussed previously, the equilibrium moisture content of filled hard gelatin capsules is significantly lower than that of empty hard gelatin capsules because of the presence of the filler. At 51% RH, empty hard gelatin capsules absorbed about 15% moisture (w/w based on empty capsule), while filled hard gelatin capsules absorb only about 3–5% moisture (w/w based on filled capsule). The equilibrium moisture content of filled hard gelatin capsules at all investigated RH conditions was in the order of Avicel® PH101 > lactose > Avicel® PH 112 > mannitol, respectively.

The vacuum-dried, brittle capsules, therefore, have to be protected from moisture by proper packaging. Mannitol-filled (250 ± 10 mg) brittle hard gelatin capsules were stored in three different packages: plastic bottles, plastic bottles with silica gel in the lid and inside the bottle and closed glass vials with silica gel inside the vial. The critical moisture value for brittleness was exceeded when the capsules were stored without packaging of simple plastic bottles without silica gel desiccant at relative humidities of 51 or 75% (Table 6). In contrast, plastic bottles or glass vials with silica gel inhibited a significant moisture uptake; the brittleness of the capsules was maintained for the study period of 6 months. Aluminum foil over-wraps or aluminum blister packs can be also used as packaging materials.

Table 6
Moisture uptake of vacuum-dried hard gelatin capsules (filled with mannitol; 250 ± 10 mg) placed in different containers

Storage	Packaging			
	Open	Plastic bottle	Plastic bottle (silica gel)	Glass vial (silica gel)
6 Months desiccator	0.3 ± 0.2	0.3 ± 0.2	0.2 ± 0.1	0.1 ± 0.0
6 Months 51% RH	3.9 ± 0.3	3.2 ± 0.3	0.6 ± 0.1	0.4 ± 0.1
6 Months 75% RH	5.0 ± 0.7	4.4 ± 0.4	0.9 ± 0.3	0.5 ± 0.1

4. Conclusion

Fast disintegrating dosage form based on perforated or dehydrated conventional hard gelatin capsules was prepared. Low dose loading and poor taste masking can be overcome by using these dosage forms, due to various filling volume of capsules. The size of holes on the shell has to be smaller than the particle size of excipient and the location of holes can vary. Vacuum drying enabled low temperature evaporating for hard gelatin capsules. Low dose loading and poor taste masking can be overcome by using these dosage forms, due to various filling volume of capsules. Dehydrated hard gelatin capsules have to be filled with non-hygroscopic or prior dried excipients to avoid any moisture transfer from filler to the capsule shell. These capsules are able to rupture in oral cavity because of their mechanical weakness. In addition, a moisture protected packaging system (like for freeze dried tablets) is necessary for these capsules.

References

[1] H. Seager, Drug delivery products and the zydis fast-dissolving dosage form, J. Pharm. Pharmacol. 50 (1998) 375–382.
[2] K. Cremer, Orally Disintegrating Dosage Forms, Pharma Concepts, GmbH & Co. KG, 2001.
[3] P. Kearney, The Zydis oral fast-dissolving dosage form, in: Rathbone, Hadgraft, Roberts (Eds.), Modified-Release Drug Delivery Technology, Marcel Dekker, 2002, pp. 191–201.
[4] A. Clarke, E.S. Johnson, N. Mallard, T.H. Corn, A. Johnston, M. Boyce, S. Warrington, D.G. MacMahon, A new low-dose formulation of selegiline: clinical efficacy, patient preference and selectivity for MAO-B inhibition, J. Neural Transm. 11 (2003) 1257–1271.

[5] S. Corveleyn, J.P. Remon, Formulation and production of rapidly disintegrating tablets by lyophilisation using hydrochlorothiazide as a model drug, Int. J. Pharm. 152 (1997) 215–225.
[6] S.I. Pather, R.K. Khankari, D.V. Moe, Orasolv and durasolv: efficient technologies for the production of orally disintegrating tablets, in: Rathbone, Hadgraft, Roberts (Eds.), Modified-Release Drug Delivery Technology, Marcel Dekker, 2002, pp. 203–216.
[7] S.V. Sastry, Recent technological advances in oral drug delivery—a review, Pharmaceutical Science & Technology Today 3 (2000) 138–145.
[8] S.R. Cherukuri, Process for forming quickly dispersing comestible unit and product there from, US Patent 5,587,172, 1996.
[9] W. Habib, R. Khankari, J. Hontz, Fast-dissolve drug delivery systems, Crit. Rev. Ther. Drug Carrier Syst. 17 (2000) 61–72.
[10] Shionogi Qualicaps product brochure, 1998, Gelatin/PEG capsules. SQ 005-1998E
[11] B.E. Jones, Hard Capsules Development and Technology, K. Ridgway Chap. Pharmaceutical Press, London, 1987.
[12] M.J. Kontny, Gelatin capsule brittleness as a function of relative humidity at room temperature, Int. J. Pharm. 54 (1989) 79–85.
[13] W. Fahrig, U. Hofer, Die Kapsel, Wiss. Verlagsges, GmbH, Stuttgart, 1998.
[14] D. Savio, P.C. Harrasser, G. Basso, Softgel capsule technology as an enhancer device for the absorption of natural principles in humans, Arzneim.-Forsch./Drug Res. 48 (1998) 1104–1106.