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A scintigraphic investigation of the disintegration behaviour of capsules in fasting subjects: A comparison of hypromellose capsules containing carrageenan as a gelling agent and standard gelatin capsules

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ABSTRACT

Two-piece hard shell capsules made from hypromellose (or hydroxypropyl methylcellulose, HPMC) have been proposed as an alternative to conventional gelatin capsules for oral drug delivery; however, little is known about their in vivo behaviour. The aim of this study was to compare the disintegration of HPMC and gelatin capsules in fasted human subjects using the technique of gamma scintigraphy. HPMC capsules containing carrageenan as a gelling agent (QUALI-V®, Qualicaps) and gelatin capsules (Qualicaps) of size 0 were filled with a lactose-based mixture. The capsules were separately radiolabelled with indium-111 and technetium-99m. Both capsules were administered simultaneously with 180 ml water to eight healthy male subjects following an overnight fast. Each volunteer was positioned in front of the gamma camera and sequential 60 s images were acquired in a continuous manner for 30 min. No differences in the oesophageal transit of the two types of capsules were noted, with the capsules arriving in the stomach in a matter of seconds. All the capsules disintegrated in the stomach. The mean (±S.D.) disintegration time for the HPMC capsules was 9 ± 2 min (range 6–11 min). The corresponding mean time for the gelatin capsules was 7 ± 4 min (range 3–13 min). These disintegration times were not significantly different ($P = 0.108$, paired t-test). In conclusion, HPMC and gelatin capsules show rapid and comparable in vivo disintegration times in the fasted state. HPMC capsules containing carrageenan as a gelling agent therefore offer a practical alternative to gelatin capsules as an oral drug delivery carrier.

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1. Introduction

Capsules have been made from gelatin since they were first patented by Mr. Mothes in Paris in 1834 as an edible container to mask the taste and odor of medicines (Jones, 2004a). They were an immediate commercial success and as a result other workers tried to get around the patent that lead to the production of the gelatin film-coated pill and the two-piece hard capsule. They tried also to find gelatin alternatives but this was more difficult because of the need to have certain specific physico-chemical properties. Gelatin solutions change from a sol to the gel state when the temperature falls below about 35 °C. Thus homogeneous films can be formed on metal mould pins, at 22 °C, by simply dipping them into hot gelatin solutions, at 50–55 °C (Jones, 2004b). The equipment to manufacture two-piece capsules has been designed around this property. Gelatin substitutes are thus required to have similar properties in order to use the same process and thus avoiding the large expenditure that would be required to develop a new process. In more recent times the stimulus to find gelatin alternatives has come from looking for materials from non-animal sources to overcome religious and dietary restriction and to overcome the problems of gelatin associated with its high moisture content (13–16%) and instability when stored at *ICH* (*International Conference on Harmonisation*) accelerated storage conditions (Ogura et al., 1998).

Hypromellose, HPMC, a widely acceptable cellulose derived material, has proven to be a polymer whose solution properties can be relatively simply modified so that it can be used to produce hard two-piece capsules on standard manufacturing machines. The Japanese company, Shionogi Qualicaps were the first to patent a system using hypromellose solutions to which carrageenan was added as a network former and potassium chloride as a gelation promoter (Ogura et al., 1998). Since then another company has patented similar systems based on the use of another polysaccharide (gellan gum) and citric acid/EDTA (Cole et al., 2004).

HPMC capsules have low moisture content (4–6%); they do not become brittle when exposed to low humidities; they are chemically stable and do not cross-link. Nevertheless, for HPMC capsules to be used as a replacement for gelatin ones they need to have similar solubility properties both in vitro and in vivo. The work by Cole et al. (2004) showed that capsules made using gellan gum remained practically intact with very little drug release in acid conditions (pH 1.2). This was in contrast to the work of Nagata et al. using capsules made with carrageenan who found comparable dissolution of paracetamol from HPMC and gelatin capsules (Nagata et al., 2001)

Previous studies to measure the in vivo disintegration properties of HPMC capsules have used gamma scintigraphy (Cole et al., 2004; Honkanen et al., 2004; Tuleu et al., 2002). The study by Cole et al. (2004) found that there was a significant difference in the in vitro and in vivo disintegration times of HPMC capsules made using gellan gum compared to gelatin capsules: HPMC capsules released the drug slower than gelatin capsules. An in vivo study by Honkanen et al. (2004) used HPMC capsules made using carrageenan filled with prolonged release formulations based on different viscosity grades of HPMC powder to measure their in vivo performance. This prolonged release diluent governed the long disintegration time observed in this study. Tuleu et al. (2002) as part of a study to deliver an active to the colon using coated capsules carried out a simple in vivo scintigraphic disintegration test using HPMC capsules, made with carrageenan, containing two radio-labelled pellets. This showed that uncoated capsules disintegrated within 10 min in each of the seven volunteers. However, it was not possible to determine the exact disintegration time of the capsules as scintigraphic images were acquired at 10 min intervals. The present study was undertaken to determine accurately the rupture times of HPMC capsules formed using carrageenan and conventional gelatin capsules in the fasted state using scintigraphy.

2. Materials and methods

2.1. Materials

Lactose monohydrate was purchased from Wako Pure chemical Industries Ltd. (Japan). Croscarmellose sodium was obtained from Mintgai Chemical (Japan). Opaque white size 0 gelatin and HPMC (QUALI-V®) capsules were provided by Qualicaps, Japan. The radio-isotopes technecium-99m (^{99m}Tc) and indium 111 (^{111}In) were purchased through Amersham (UK) as complexes with diethylenetriamine pentaacetic acid (DTPA).

2.2. Capsule filling and radiolabelling

The capsules contained a diluent (lactose) and a disintegrant (croscarmellose sodium). The powder for filling was mixed for 10 min in a Turbula mixer. On the day of the study, 450 mg of this mixture was weighed, compressed to form a plug at 70 N using a Höfliger and Karg powder plug test rig (Jones, 1998). The powder plugs produced were transferred into size 0 HPMC or gelatin capsules after the capsules had first been radiolabelled by putting 2× 25 mg of radiolabelled lactose either with ^{99m}Tc or with ^{111}In, in the body and the cap ends of the capsules. The lactose was radiolabelled by adding a few drops of ^{99m}Tc or with ^{111}In solutions with a syringe per 25 mg and drying this powder in an oven. The final capsule powder fill weight was 500 mg of which 10% was croscarmellose sodium. The level of radioactivity on the day of the study was a mean of 3.75 MBq (±1.40) MBq for ^{99m}Tc and a mean of 0.20 (±0.01) MBq for ^{111}In. HPMC capsules were always labelled with ^{99m}Tc and gelatin capsules with ^{111}In. This arrangement made it possible to identify the position of the capsules within the gastrointestinal tract and also their sites of disintegration.

2.3. Subjects and study protocol

Eight healthy male volunteers (mean age 27 years ranging from 20 to 34 years, mean weight 71 kg and ranging from 55 to 95 kg) participated in the study. The single blind study was separately approved by the Joint UCL/UCLH Committees on the Ethics of Human Research and by the Administration of Radioactive Substance Advisory Committee and followed the tenets of the Declaration of Helsinki (1964) and its subsequent revisions. Each of the volunteers received, following an overnight fast, an HPMC and gelatin capsule with 180 ml water

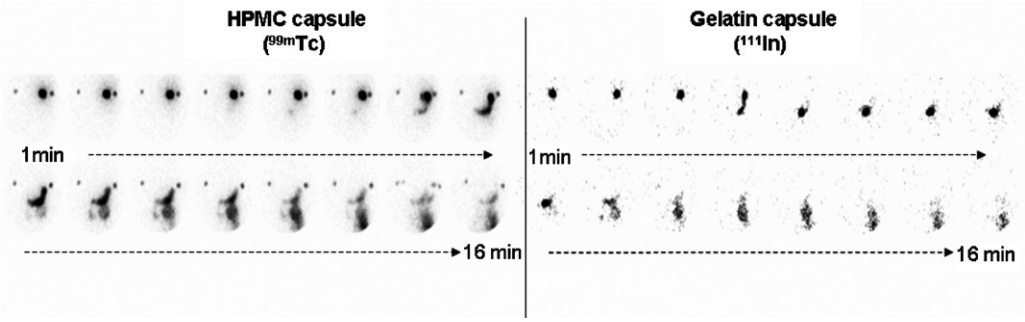

Fig. 1 – Gamma scintigraphic images sequence acquired for a representative volunteer.

in an upright position and remained so for the gamma camera measurements.

Disintegration of the capsules was followed using a gamma camera. A single-headed gamma camera (model 400AC, General Electrics Medical Systems, Milwaukee, USA) with a high performance detector with a 40 cm diameter field of view and capable of simultaneous data acquisition was used for this purpose. The detector was fitted with a medium energy parallel hole collimator suitable for simultaneous ^{99m}Tc and ^{111}In imaging. Two external markers containing ^{99m}Tc each less than 0.5 MBq were taped to each side of the volunteer in order to assist with anatomical localisation of the capsule. The subjects stood still in front of the head of the gamma camera and dynamic images of 60 s duration were acquired continuously for up to 30 min post dose.

2.4. *Analysis and quantification of scintigraphic data*

The scintigraphic images were processed using a computer system (model 3200i, General Electric Medical Systems, Milwaukee, USA). Counts were obtained for the total capsule at each time point via region-of-interest analysis. Capsule disintegration was assessed by visualising the spread of radioactivity. The time of the first image highlighting the spread of radioactivity from the 'core' of the capsule was taken and recorded as the initial capsule disintegration time.

3. Results and discussion

On swallowing, both types of capsules moved rapidly down the oesophagus into the stomach, within a time frame of 10–20 s. No difference in the transit of the HPMC and gelatin capsules was noted. Oesophageal transit for hard gelatin capsules has been reported to range from 7 to 24 s (Bailey et al., 1987; Batchelor, 2005; Perkins et al., 1994; Wilson et al., 1988). The results from the present study are in good agreement with these published data for gelatin capsules. Cole et al. (2004) reported that the oesophageal transit of gelatin and HPMC capsules made from gellan gum was very rapid in the majority of the volunteers (<20 s). However, Honkanen et al. (2004) have reported that HPMC capsules made from carrageenan have a tendency to adhere to the oesophagus; capsules lodged in the oesophagus for 22–143 min in 4 out of 12 administrations to human subjects. The authors explained that it happened on the first day of a two-way cross-over study and the four incriminated volunteers may not have taken enough water whilst ingesting the capsule. No such observations of prolonged oesophageal transit were noted in the present study and this could be due to strict guidelines for the swallowing phase (ingestion of capsules with 180 ml of water in an upright position and remaining so).

Fig. 1 represents gamma scintigraphic images sequence acquired for a representative volunteer. The HPMC and gelatine capsules were labelled with two different radio-isotopes (respectively ^{99m}Tc and ^{111}In). Because the collimator was fitted with a medium energy collimator simultaneous visualisation on two parallel screens (on the left for ^{99m}Tc and on the right for ^{111}In) of the fate of the two capsules was possible as illustrated on the left and right side of Fig. 1. The two ^{99m}Tc radiolabeled external markers for anatomical localisation of the capsules can be seen on the left side of Fig. 1. The time at which disintegration of the capsules starts was recorded when spread of radioactivity was observed along with decreasing intensity of the core. It should not be confounded with the movement of the capsule in the stomach as seen at 4 min for gelatin capsule. All the capsules disintegrated in the stomach. The individual and mean disintegration times for the HPMC and gelatin capsules are presented in Table 1. The mean disintegration time for the gelatin capsules was 7 ± 4 min (range 3–13 min). These disintegration results are in good agreement with previous findings using gamma scintigraphy (Brown et al., 1998; Cole et al., 2004; Digenis et al., 2000). The corresponding mean disintegration time for the HPMC capsules was 9 ± 2 min (range 6–11 min). No significant difference in disintegration times between the capsules was

Table 1 – Disintegration times for hypromellose and gelatin capsules

Volunteer	HPMC capsules	Gelatin capsules
1	9	11
2	6	4
3	7	7
4	11	13
5	10	4
6	8	5
7	11	7
8	8	3
Mean ± S.D. (min)	9 ± 2	7 ± 4

noted $P = 0.108$, paired t-test. Interestingly, while the mean disintegration of the HPMC capsule was fractionally longer than its gelatin counterpart, the spread of individual disintegration times for the HPMC product was tighter suggesting more consistent in vivo behaviour. Honkanen et al. (2001) conducted a pharmacokinetic study using ibuprofen as a model drug and reported that HPMC capsules processed using carrageenan and gelatin capsules were bioequivalent. However, the HPMC product used in the study by Honkanen et al. was of food grade and contained a higher quantity of carrageenan than the capsule used in the present study (pharmaceutical grade). Overall, it can be concluded from the current scintigraphic study that HPMC capsules made using carrageenan and gelatin capsules can be used interchangeably in the fasted state.

Cole et al. (2004) have reported a very long mean disintegration time for HPMC capsules containing gellan gum as a gelling agent in the fasted state (28 min). This disintegration time has implications for the delivery of immediate release medicaments and is significantly longer than the mean time obtained in the present study (9 min). Thus indicating that HPMC capsules made with carrageenan are the preferred capsules for such products.

While imaging techniques such as gamma scintigraphy provide unequivocal evidence for dosage form performance in vivo, there is still a role for in vitro testing to help elucidate the underlying mechanisms involved in capsule release as well as factors affecting their behaviour. HPMC capsules dissolve and disintegrate in a different way to gelatin capsules. For example, in simple acidic and simulated gastric media using the ball bearing release test, the shell dissolution of empty HPMC capsules containing carrageenan was slower than empty gelatin capsules (Chiwele et al., 2000). Podczeck and Jones (2002) conducted a comparative dissolution study with HPMC made using carrageenan and gelatin capsules, using theophylline as a model compound. The authors observed that the first split in the capsule shell took longer to occur for the HPMC product than for gelatin. They also noted that after the first split, the remaining film dispersed more rapidly for HPMC capsules than for gelatin because once the carrageenan network was disrupted, the film could dissolve more easily. This may have been the reason why in the in vivo study the disintegration times for HPMC capsules were less variable. Another study (Tochio et al., 2002) showed that the dissolution of paracetamol from HPMC capsules was not extensively influenced by the pH of the test fluids but rather by the concentration of potassium ions (if over 12.5 mM) and of total ions (if over 355 mM) with HPMC capsule containing carrageenan. In water, dissolution of HPMC capsules made with gellan gum was identical to that of gelatin whereas in acid conditions and the presence of K^+ cations hindered the HPMC capsule opening (Cole et al., 2004). These effects are related to the fact that gellan gum is insoluble at pH < 4.0 (Cole et al., 2004) whereas carrageenan is readily soluble at pH 1.2, which explains why these two types of HPMC capsules can not be considered equivalent in vivo.

4. Conclusions

This study has shown that HPMC capsules made using carrageenan as a gelling agent and gelatin capsules show rapid and comparable disintegration times in the fasted state. This type of HPMC capsule product can therefore be considered a viable alternative to gelatin capsules for drug delivery to the gastrointestinal tract. Further studies are required to assess the performance of this capsule in the fed state.

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