The disintegration behaviour of capsules in fed subjects: A comparison of hypromellose (carrageenan) capsules and standard gelatin capsules

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ABSTRACT

Two-piece hard shell capsules made from hypromellose (or hydroxypropyl methylcellulose, HPMC) containing carrageenan as a gelling agent have been proposed as an alternative to conventional gelatin capsules for oral drug delivery. We have previously compared the disintegration of hypromellose$_{carrageenan}$ (Quali-V®) and gelatin capsules (Qualicaps) in fasted human subjects using the technique of gamma scintigraphy. This second study used the same technique with both fasted and fed human subjects. Size 0 capsules were filled with powder plugs made from lactose and did not contain croscarmellose as in the original study. 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. The mean (±S.D.) disintegration time in the fasted state for the hypromellose$_{carrageenan}$ capsules was 8 ± 2 min and for gelatin 7 ± 3 min. These results were not statistically different from the data in the original study and show that the removal of the croscarmellose had no effect on the results. The mean (±S.D.) disintegration time in the fed state for the hypromellose$_{carrageenan}$ capsules was 16 ± 5 min and for the gelatin capsules was 12 ± 4 min. There was no statistical difference between the hypromellose$_{carrageenan}$ and gelatin capsules in either the fed or fasted state.

1. Introduction

Hypromellose capsules containing carrageenan as a gelling agent were first introduced into the market by Qualicaps, then part of the Shionogi Company, in the late 1990s. They were introduced into the market to overcome some of the inherent problems of gelatin capsules: animal origin of the raw material, brittleness at low humidities or when filled with hygroscopic formulations, crosslinking after storage at ICH accelerated conditions and high moisture content (13.0%–16.0%), which can affect labile actives. However, hypromellose capsules differ from gelatin capsules in that their composition depends upon the manufacturer of the shells. This is because the formulations and method of manufacture are patented and results in capsule shells with differing properties, which means that are not interchangeable. How has this come about? In order to use the standard gelatin capsule manufacturing machines for their manufacture two aspects need to be changed. One method involves converting hypromellose solutions into a gelling system similar to gelatin by the addition of a gelling agent. The system used for standard release pharmaceuticals is based on the addition of carrageenan as a network former and potassium chloride as a network promoter: carrageenan is soluble at acid pH (Ogura et al., 1998). Another patented gelling agent is gellan gum, which is poorly soluble pH <4.0, and these capsules behave differently from gelatin capsules in the stomach (Cole et al., 2004). The other method is to modify the machines to reverse the normal dipping process conditions from dipping a cold pin into a hot solution to dipping a hot pin into a cold solution. This process makes use of the fact that the viscosity of hypromellose solutions increases at higher temperatures. This process, first patented by Eli Lilly & Co in 1950 for manufacturing methyl cellulose capsules (Murphy, 1950), involves extensive machine modifications in order to heat the mould pins prior to dipping and after dipping to maintain the pin temperature during drying until the films are dry enough to make them immobile. Hypromellose capsules manufactured by this method have been patented recently by Pfizer (Pfizer Products Inc., 2008). Their dissolution is not influenced by pH and the published dissolution data available shows them to be

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inferior to hypromellose capsules containing carrageenan (Pfizer Products Inc., Uyama et al., 2010). There is a need to understand how hypromellose$_{carrageenan}$ capsules perform in vivo to enable formulators to make better use of their technical properties. They have already been used by the pharmaceutical industry for registered medicinal products in Japan, Europe and the USA.

The first part of this study compared the in vivo disintegration of hypromellose capsules containing carrageenan and standard gelatin capsules in fasted subjects (Tuleu et al., 2002). In this second part, the influence of food on capsule disintegration will be examined. The same materials and methods will be used except for the formulation of the powder fill. Croscarmellose (10%), a superdisintegrant, was included with lactose in the formulation. The reason for its inclusion was that this mixture had been used by Shionogi, former owners of Qualicaps, as part of a standard formulation used in many published dissolution studies (Nagata et al., 2001, Ogura et al., 1998; Sakaeda et al., 2002; Tochio et al., 2002). It was decided to include it so that a comparison could be made with historic data. However, it could be speculated that the inclusion of a high level of disintegrant might have an influence on the disintegration time. Therefore in this study no disintegrant was included and lactose monohydrate was the sole component of the capsule fill.

The study was conducted in two steps. Firstly the in vivo disintegration time for hypromellose and gelatin capsules was measured using fasting subjects. This was to check that the results were not affected by the removal of croscarmellose from the fill formulation. Secondly the same subjects were tested after they had eaten a standard breakfast to measure the effect of food on disintegration.

2. Materials and methods

2.1. Materials

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

2.2. Capsule filling and radiolabelling

The capsules contained lactose which was passed through a 100 μm mesh screen prior to use. On the day of the study, 450 mg of lactose was weighed and compressed to form a plug at 70 N using a Bosch (Höfliger and Karg) type powder plug test rig (Jones, 1998). The powder plugs produced were transferred into size 0 hypromellose 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. The level of radioactivity on the day of the study was a mean of 3.75 MBq (±0.65) MBq for ^{99m}Tc and a mean of 0.20 (±0.01) MBq for ^{111}In. Hypromellose capsules were always labelled with ^{99m}Tc and gelatin capsules with ^{111}In. This arrangement made it possible to identify simultaneously 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 24 years ranging from 19 to 27 years, mean weight 68 kg ranging from 61 to 76 kg) participated in the study. The single blind study was separately approved by the USM committee on the Ethics of Human Research and followed the tenets of the Declaration of Helsinki (1964) and its subsequent revisions. In the first part of the study the volunteers fasted overnight. In the second part of the study the volunteers ate a standard light breakfast (30 g of corn flakes, 150 ml of half fat milk, 2 slices of toast, a tablespoon of margarine and 2 tablespoons of jam: ~500 kcal). There was a wash out period of seven days between part 1 and part 2. On the measurement days all the volunteers received a hypromellose and a gelatin capsule with 180 ml of water in an upright position and remained so for the gamma camera measurement.

Disintegration of the capsules was followed using a gamma camera. A single-headed gamma camera (model 400AC, General Electric 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, both less than 0.5 MBq were taped each side of the volunteer in order to assist with anatomical localisation of the capsule. The subject 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, i.e. the release of the capsule contents through the first split in the shell wall. The mean, standard deviation and median times were calculated ($n = 8$). A paired two tailed t test (p 0.05) was used to compare the disintegration of the 2 types of capsules, in fed and fasted states.

3. Results and discussion

All the capsules disintegrated in the stomach. In the fasted state the results shown in Table 1 were not statistically different from the results reported in our previous paper (Tuleu et al., 2002): hypromellose capsules mean (±S.D.) was 9 ± 2 min and gelatin 7 ± 4 min. This demonstrates that the omission of the disintegrant, croscarmellose sodium, had no effect on the results. An American survey carried out in 1992 to find the excipients of choice used in tablet and capsule formulations found that 60% of respondents stated that they would use disintegrants and wetting agents (Shangraw and Demarest, 1993). The authors of this report commented that this usage was influenced by the Food and Drug Administration's emphasis on dissolution testing. No mention

Table 1
Disintegration times (min) for hypromellose and gelatin capsules, in the fasted state.

Volunteer	Hypromellose capsules	Gelatin capsules
1	12	8
2	5	6
3	9	11
4	9	9
5	10	4
6	5	8
7	8	4
8	7	9
Mean ± S.D. (min)	8 ± 2	7 ± 3

Table 2
Disintegration times (min) for hypromellose and gelatin capsules, in the fed state.

Volunteer	Hypromellose capsules	Gelatin capsules
1	19	11
2	15	13
3	9	8
4	25	8
5	17	21
6	13	11
7	11	16
8	15	10
Mean ± S.D. (min)	16 ± 5	12 ± 4

was made of improved in vivo performance. Likewise in Europe the inclusion of disintegrants in capsule formulations only became common practice during the 1990s as dissolution requirements became more widespread (Jones, 1995).

Table 2 shows the results obtained in the fed state: the disintegration times were for gelatin capsules 12 ± 4 min and 16 ± 5 min for hypromellose capsules. Both capsules showed an increase in their disintegration times. There was no statistical difference between the hypromellose and gelatin capsules in fed or fasted state.

In fed studies the amount and type of food can have a significant impact on the results. The study by Cole et al. (2004) used a standardised high fat meal with a significantly higher calorie content (1300 kcal) than used in the present study. In this study the authors were interested in measuring more than just the capsule disintegration time. They wanted to measure gastric emptying and the food was radiolabelled to enable them to follow this transit. Thus they chose a meal that needed more digestion than the more typically British breakfast used in our study.

The results for gelatin capsules found in our study are comparable to other values reported in the literature that measured the disintegration using gamma scintigraphy. The first reported study used capsules filled with either a soluble or an insoluble formulation and two fasted subjects: it reported 6 min for the soluble fill and 30–40 min with the insoluble fill (Casey et al., 1976). More recent studies have used fill formulations more in keeping with standard practices and the modern devices to detect more precisely the first opening of the capsule shell wall (Brown et al., 1998; Digenis et al., 2000; Cole et al., 2004; Gao et al., 2007). The results from these 3 studies found for the fasted state 'initial disintegration times' of 8 ± 2, 7 ± 2, 8 ± 4 and 11 ± 6 min respectively.

There is less literature available on hypromellose capsules to be able to compare these results. This issue is compounded by the fact that the formulation of hypromellose capsules depends upon the manufacturer, because the shell formulations are patented. The first study using hypromellose$_{carrageenan}$ capsules found that all capsules disintegrated within 10 min, the time of the first camera shot in their study (Tuleu et al., 2002). Capsules that use gellan gum as the network former have been shown to take longer to disintegrate, recorded as the 'initial disintegration', in vivo in both the fed and fasted states, 28 ± 10 min and 60 ± 22 min, respectively. The authors explained this on the fact that the pK_a of gellan gum is 3.4 and thus it is poorly soluble at acid pH (Cole et al., 2004).

In vitro disintegration times for gelatin and hypromellose capsules have been published. The problem with this measurement is that the rate controlling step is the nature of the fill material (Jones, 1972). One method using capsules filled with a ball bearing has been used to avoid the effect of the fill material (Boymond et al., 1966; Jones and Cole, 1971; Chiwele et al., 2000). This measures the time for the ball bearing to fall from the capsule after immersion in the test medium which represents the time for the first rupture. Chiwele et al. (2000) compared 2 types of gelatin capsule, standard and ones containing 5% PEG 4000, with hypromellose$_{carrageenan}$

capsules and found that at 37 °C the release rate was about 90 s for both gelatin capsules and about 250 s for the hypromellose capsules. This being explained by the lower moisture permeability of hypromellose compared to gelatin thus the polymer taking longer to hydrate before it can start to dissolve. They tested capsules over the temperature range 10–55 °C: the shell dissolution times of hypromellose capsules did not change whereas the times for both gelatin capsules increased as the temperature deceased from 37 °C and below about 25 °C they were insoluble. It was recommended that hypromellose capsules be taken with a cold drink and gelatin capsules with a hot drink. The official Pharmacopoeial apparatus was not designed for the easy viewing of the course of capsule disintegration. Missaghi and Fasshi (2006) used the USP apparatus and end point to measure the disintegration time, i.e. "all of the capsules have disintegrated except for fragments from the capsule shell", for powder filled capsules and thus very different from rupture times. In a pH 1.5 hydrochloric acid solution at 37 °C, the disintegration times were 151.7 ± 3.6 s for hypromellose$_{carrageenan}$ capsules and 34.0 ± 3.6 s for gelatin. They observed that these hypromellose capsules had a longer lag time than the gelatin capsules before the first split. After this the hypromellose capsules tended to disperse uniformly over their whole surface whereas the gelatin ones opened at the ends leaving a tube and it took longer for the contents to be exposed to the dissolution media. A similar observation had been reported previously by Podczeck and Jones (2002). El-Malah et al. (2007) devised a novel method to visualise the rupture time of hypromellose capsules by using real-time dissolution spectroscopy. They used USP apparatus II fitted with a fibre-optic dip-probe connected to a rapid scanning high-performance UV spectrophotometer. They compared two types of hypromellose$_{carrageenan}$ capsule, a nutritional and a pharmaceutical grade. The capsules were filled with caprylocaproyl macrogol-8 glycerides EP (Labrasol), which could be detected in the dissolution medium. In simulated gastric fluid at 37 °C the rupture times were 3.6–4.8 min for the pharmaceutical grade and 9.67–11.25 min for the nutritional grade. In vivo there was no statistical difference in the dissolution/disintegration between the gelatin and hypromellose$_{carrageenan}$ capsules. The reason for this could be due to effect the temperature of the water used to take the capsules in our study. The water in the stomach would need to be warmed to over 25 °C before the gelatin ones could start to dissolve and this would erode some of the time differences seen in the in vitro testing.

Another factor involved could be the activity of the stomach after the capsules have been taken. Kamba et al. (2000) investigated the mechanical destructive force on dosage forms in the stomach. To do this they made tablets with different crushing strengths: tablet cores containing riboflavin were coated with an ethanol/acetone solution of polyvinylacetal diethylaminoacetate, which only dissolves in an acidic environment, and this was compressed inside a tablet made of Teflon® powder, the strength of which was regulated by the compression force and the grade of powder used. The tablets, filled inside size 00 gelatin capsules, were administered to volunteers, either fasted or fed. The site of tablet breakage/disintegration was indicated by the increase of riboflavin in the urine. They found that the force to break the tablets was stronger in the fed state than the fasted due to the different types of contraction of the stomach wall during these periods. Tests on tablets with a crushing strength of 1.5 N found that in the fed state 4 out of 4 were broken and in the fasted state 3 out of 5. The same group, Kamba et al. (2003), performed a similar set of experiments to determine the forces involved during in vitro disintegration and dissolution testing. They prepared core tablets of benzoic acid and coated them on 3 sides with a mixture of ethyl cellulose and carnauba wax. They found that the highest forces exerted on the tablets were in the disintegration apparatus and that these were significantly weaker than the mechanical destructive force

produced by normal movements in the GI tract. Thus when gelatin and hypromellose$_{carrageenan}$ capsules are taken with a draft of water the difference in dissolution times in acid media seen in vitro do not occur in vivo because of the mechanical activity of the stomach.

A new method has recently been published of predicting the in vivo performance of capsules using an in vitro dynamic gastric model (DGM), which mimics the mechanical movements and the liquids secreted during digestion of the stomach and duodenum (Vardakou et al., 2011). Three types of capsules were compared, gelatin, hypromellose$_{carrageenan}$ and hypromellose$_{gellan}$. The in vitro capsule rupture times were measured using a USP dissolution apparatus no. 1 in artificial gastric juice (BP) without pepsin: the rupture times were 3.13 ± 0.48 min, 6.50 ± 1.00 and 18.0 ± 5.2, respectively. The in vitro rupture times were also measured using the DGM with media to represent the stomach fasted state with solutions to mimic gastric secretions and the fed state after the ingestion of a high fat breakfast. The rupture times for the hypromellose$_{carrageenan}$, gelatin and hypromellose$_{gellan}$ capsules in the fasted state were 3.86 ± 1.84 min, 5.33 ± 1.03 and 9.33 ± 1.03 and in the fed state were 85 ± 18.94 min, 75 ± 16.7 and 79 ± 11.00, respectively. These results are somewhat different to the in vivo capsule disintegration data presented in this paper and elsewhere (Cole et al., 2004) and highlight the difficulty of using in vitro models to simulate the complexity of the human gastrointestinal tract.

4. Conclusion

This study of the in vivo disintegration behaviour of gelatin and hypromellose$_{carrageenan}$ capsules in subjects in the fed state complements our previous study in the fed state. Both capsules have similar performances in vivo. Hypromellose$_{carrageenan}$ capsules can be considered as an alternative to gelatin capsules for pharmaceutical products as they have similar in vivo properties with the additional advantage of avoiding their well-known drawbacks.

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