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Research Paper

Polymer film formulations for the preparation of enteric pharmaceutical capsules

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Abstract

Objectives Standard pharmaceutical capsules are designed to dissolve in the acidic environment of the stomach releasing the encapsulated contents for absorption. When release is required further along the gastrointestinal tract capsules can be coated with acid insoluble polymers to enable passage through the stomach and dissolution in the intestine. This paper describes formulations that have the potential to be used to produce two-piece hard capsules for post-gastric delivery without the requirement of an exterior coat.

Methods The formulation uses three polysaccharides: sodium alginate, hypromellose and gellan gum to provide acid insolubility and the ability to form capsules using standard industrial equipment.

Key findings The rheological profile, on cooling, of the base material, water content and thickness of the films were shown to be comparable with those of commercial capsules. The capsules remained intact for 2 h in 100 mM HCl at pH 1.2, and within 5 min of being removed from the acid and submerged in phosphate-buffered saline at pH 6.8 were ruptured.

Conclusions Selected formulations from this study have potential for use as delayed release capsules.

Keywords hard capsule; polymer film formulation; post-gastric delivery

Introduction

Encapsulation using a premoulded, two-piece hard capsule is just one of a multitude of drug delivery systems in practice and is extremely effective in delivering active pharmaceutical ingredients (APIs). Standard pharmaceutical hard capsules are generally manufactured from gelatin. However, religious and ethical objections to the use of animal-based material in capsules forced pharmaceutical companies to consider alternatives. This has led to several alternatives to the gelatin capsule being developed[1–3] and available on the market, most notably Shionogi Quali-V and Capsugel V-Caps. Both of these capsules are based on hypromellose (HPMC) and studies have shown that HPMC capsules are promising as far as regulatory, manufacturing, religious and dietary issues are concerned.[4] Capsules are prepared industrially by dipping stainless-steel mould pins into a solution of gelatin or HPMC containing a gelling agent. The mould pins are subsequently removed, inverted and dried to form a film on the surface. The dried capsule films are then removed from the moulds, cut to the correct length and then caps and bodies are assembled, printed and packaged.[5–7]

Gelatin and HPMC capsules are designed to dissolve in the stomach, releasing the encapsulated contents for absorption in the intestine following gastric emptying. However, certain APIs are unsuitable for gastric release; such drugs may be irritant to the gastric mucosa, unstable or reactive at stomach acid pH, may interfere with gastric metabolism or the drug target may be further along the gastrointestinal tract. If passage through the stomach for post-gastric delivery is required using a capsule, methods have been developed where the loaded gelatin or HPMC capsule is coated with an acid insoluble polymer, usually anionic polymethacrylates (Eudragit), cellulose acetate phthalate (Aquacoat) or polyvinyl acetate phthalate (Sureteric). This method of coating works effectively for HPMC capsules[8,9] and to some extent gelatin capsules, but in the case of gelatin capsules,

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poor adhesion of the coat to the smooth gelatin surface can be a problem[10] causing the capsule shell to become brittle.

Our proposed solution is a two-piece hard capsule manufactured from HPMC in combination with gellan gum and sodium alginate. These materials have bulk enteric properties, thereby avoiding the need for spray coating. The materials used in the formulation of such a capsule need to exhibit similar mechanical properties to the gelatin capsule, be compatible with the current manufacturing procedures for producing, filling and sealing the capsule, be produced from approved pharmaceutical-grade materials and pass pharmacopoeial tests for enteric capsules.

The HPMC capsule has many advantages over the gelatin capsule. It is known that substances containing aldehyde groups can react with the gelatin, forming crosslinks[11,12] rendering the capsule insoluble and brittle on storage. Indeed, there have been attempts to utilise this property to create an enteric gelatin capsule with mixed success.[13–16] Therefore to produce a non-animal-based enteric two-piece hard capsule is an attractive proposition. Moreover, there has already been success in the production of a one-piece enteric softgel capsule[17] trademarked Entericare by Banner.

HPMC in capsule formulations acts as the bulk film-forming material and a second polysaccharide (usually carrageenan or gellan gum) can be added as a gelling agent, which gels rapidly at ~35°C enabling the HPMC to hold its structure on the dip moulding pin during manufacture. This investigation expands on HPMC capsule formulations by introducing a third polysaccharide, sodium alginate, which is acid insoluble, creating a base material that can be moulded onto stainless-steel pins and once dried produces capsules with bulk enteric properties. Small deformation rheological measurements were used to monitor structural changes that occur within the tertiary polysaccharide mixtures across the temperature range of the dip moulding process, and the polymer films produced by these mixtures were tested for physical performance and in-vitro gastro-resistance.

Materials and Methods

All formulations were based on HPMC (Pharmacoat 606; Shin Etsu, Japan), sodium alginate (Protonal LFR 5/60; FMC Biopolymer, Dramman, Norway), gellan gum (Gelrite; Kelco Surry, UK) and sodium chloride as source of cations (Sigma-Aldrich, Poole, UK). The gellan gum, sodium alginate and NaCl were dissolved in deionised water at high temperature (>80°C) before dispersing HPMC into the mixed polymer solution. The mixture was stirred for 2 h until all material was fully hydrated and a homogenous dispersion was evident; this provided the base capsule material. Details of the formulations tested are given in Table 1.

Rheological analysis

Rheological analysis of the capsule base material was carried out in the linear viscoelastic region using a 40-mm parallel plate geometry mounted on a Malvern Gemini Rheometer (Malvern Instruments, UK) fitted with Peltier plate thermal control. Changes in G' (storage modulus) and G'' (loss modulus) were measured during cooling at a rate of 1°/min performed at 0.5% strain over a temperature range 80–10°C, using a fixed oscillation frequency of 1 rad/s.

Dip moulding and film casting

Polymer base mixture was cooled following preparation to 58–69°C and cap and body stainless-steel moulding pins (custom machined at Aston University) at ambient temperature were dipped into the mixture, removed and inverted to mimic the dip moulding process in industrial capsule production. A range of dipping temperatures (58–69°C) were tested to evaluate a correlation between capsule thickness and dipping temperature. Capsules were dried overnight at room temperature then removed from the moulding pin using a prototype custom machined plastic disc where the moulding pin containing the dried capsule was inserted and fitted flush to the top edge of the capsule, and on application of force the capsule was stripped off the moulding pin. The capsules were then trimmed to a length comparable with a size 00 gelatin capsule and thickness of the capsules was measured on the main body of open capsules using digital callipers. The remainder of the capsule base mixture was poured on a Perspex plate and a film was cast using a casting knife to produce films with thickness range 120–300 μm. The films were allowed to dry for 24 h at room temperature and the thickness measured (with digital callipers).

Puncture test

Puncture tests were carried out on 4-cm^2 film samples using texture profile analysis (TPA). A stainless-steel probe was

Table 1 Compositions of formulations tested

Formulation	HPMC (% w/w)	Gellan gum (% w/w)	Sodium alginate (% w/w)	NaCl (% w/w)	Capsule formed
1	19	0	0	0	No
2	19	0.1	0	0.1	Yes
3	19	0.2	0	0.2	No
4	18	0.2	1	0.2	Yes
5	17	0.2	2	0.2	Yes
6	15	0.2	5	0.2	Yes
7	15	0.2	7.5	0.2	Yes

Formulation 1 is a control sample of 19% HPMC alone from which capsules cannot be prepared as there is no gelling agent present. Formulation 2 is a second control from which standard HPMC capsules can be prepared.

applied perpendicular to the sample film surface at a constant rate of 10 mm/min until the probe ruptured the film. The maximum force (N) before rupture was recorded as an indication of the mechanical properties of the films produced as a direct comparison with standard capsules.

Water content evaluation

Analysis of water content of the polymer films was performed by thermo-gravimetric analysis (TGA) (Perkin Elmer). A sample of film was heated at 10°C/min from 50°C to 140°C and water content was calculated from the reduction in mass on completion of the heating regime. Capsule shells of commercially available gelatin and HPMC capsules were also measured using this procedure.

Enteric testing of capsules

Capsules were loaded with 100 mg of diclofenac, sealed then tested for entericity using a USP dissolution apparatus I (baskets). Capsules were placed in baskets and submerged into 900 ml 100 mM HCl at 37°C for 2 h. Following the 2-h period the media was changed from acid to phosphate-buffered saline (PBS) at pH 6.8.

Statistical methods

Statistical analysis was performed to compare mean values by using a one-way analysis of variance with post-hoc Tukey's honestly significant difference (HSD) test to identify significant differences ($P < 0.05$) between data sets.

Results

Rheological analysis

Rheological assessment of the different capsule formulations gave an indication of the potential for the formulation to gel on the dip moulding pins during industrial manufacture. A summary of the changes in storage modulus (G′) and loss modulus (G″) observed for formulations 1–7 while cooling from 80°C to 10°C is shown in Table 2. These data provide information on how the development of structure occurred during the manufacturing process.

Dip moulding and film casting

Table 1 reveals which formulations were able to form uniform films by the dip moulding process and Figure 1 shows a photograph of a capsule prepared from formulation 5 (17% HPMC, 0.2% gellan, 2% sodium alginate). Once the capsules were formed and dried, they were removed from the moulding pins using prototype capsule stripping apparatus. The thickness and uniformity of the capsules were measured and were shown to be dependent on dipping temperature (Figure 2). When the moulding pin was dipped into the capsule base material at 69°C capsules were formed that were 130 μm ± 0.6 μm thick, compared with dipping at 58° C which produced capsules that were 280 μm ± 2.3 μm.

The films were prepared using a casting knife with the capsule base mixture set at 55–60°C. This produced films within the thickness range of 120–150 μm. Table 3 provides information on the water content and force required to puncture the films. The moisture content of the developed capsule shells had values ranging from 5.1% to 9.8%, which falls between that of commercial gelatin capsules (13%) and commercial HPMC capsules (4.5%).[18]

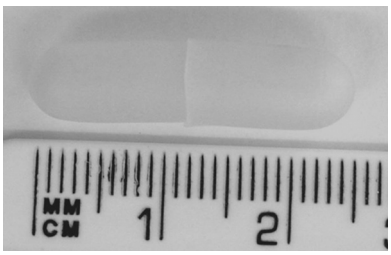

Figure 1 Capsule formed using formulation 5 (17% HPMC, 0.2% gellan gum, 2% sodium alginate)

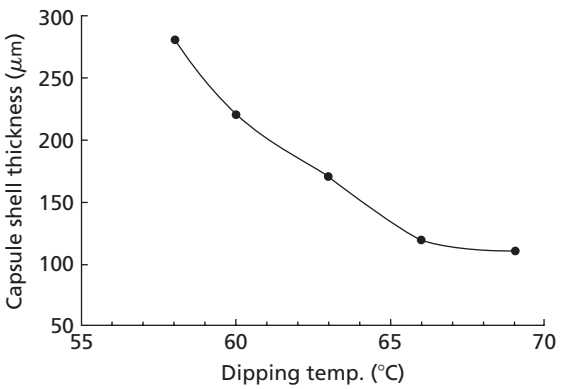

Figure 2 Dipping temperature vs capsule thickness for formulation 5 (17% HPMC, 0.2% gellan gum, 2% sodium alginate, 0.2% NaCl). Results represent mean ± SD, $n = 3$.

Table 2 Summary table showing values of G′ and G″ for capsule base formulations at 60°C, 25°C and temperature at maximum G′ on cooling at 1°C/min (1 rad/s 0.5% strain)

Formulation	G′(Pa) at 25°C	G″(Pa) at 25°C	G′(Pa) at 60°C	G″(Pa) at 60°C	Temp. at G′Max (°C)
1	0.88	8.2	14.9	13.6	48.1
2	199.0	59.1	5.0	2.3	44.4
3	25.0	33.4	5.9	2.8	44.6
4	762.4	115.7	8.9	4.3	45.0
5	464.1	274.8	3.9	2.0	43.7
6	89.1	40.0	22.3	9.0	41.6
7	819.5	225.6	39.0	21.4	33.6

Table 3 Water content and puncture force of sample film formulations

Formulation	Water content (%weight)	Puncture force (N)
Gelatin hard capsule	13.5 ± 0.2	11.1 ± 0.4
HPMC capsule	4.5 ± 0.4	8.5 ± 0.5
1	–	–
2	6.5 ± 0.9	15.8 ± 0.8
3	5.1 ± 0.6	19.2 ± 1.4
4	9.8 ± 1.1	13.1 ± 1.3
5	8.7 ± 0.6	3.2 ± 0.6
6	7.0 ± 0.9	1.2 ± 0.3
7	–	–

Results represent mean ± SD, $n = 3$.

Enteric testing of films and capsules

Initial acid resistance studies (using a 2-cm diameter piece of film as part of a seal of a weighted vial (Figure 3), submerged in 100 mM HCl) on films with a thickness of 150 μm resulted in all films being ruptured within 2 h, with formulations 5 (17% HPMC 0.2%, gellan gum, 2% sodium alginate, 0.2% NaCl) and 6 (15% HPMC, 0.2% gellan gum, 5% sodium alginate, 0.2% NaCl) approaching the 2-h requirement with a rupture time of 75 min and 85 min, respectively. Formulations 2 (standard HPMC capsule formulation) and 4 were ruptured in less than an hour (formulation 7 was too brittle to test). The presence of the sodium alginate in the 150-μm films (as in the case of formulations 4, 5 and 6) appeared to improve the resistance time. However, the requirement of 120 min for enteric films was not met by any of the films when a film thickness of 150 μm was employed (Figure 4).

A repeat study increasing the film thickness to that of an enteric coated capsule (Colpermin) 250–300 μm was then performed on formulations 2, 4, 5 and 6 (formulation 3 was not tested as it did not form a capsule by dip moulding) (Figure 4). The effect of increasing the film thickness from 150 μm to 250 μm is evident with formulation 2 (standard HPMC capsule formulation, which contains no sodium alginate) almost doubling resistance time (from 39 min to 65 min). Formulations 5 and 6, which contained 2% and 5% wt sodium alginate, respectively, passed the enteric test and remained intact for the 2-h time-frame (Figure 4). These films were then placed in pH 6.8 PBS at 37°C and the films were ruptured within 1 min. Capsules prepared from formulations 5 and 6 (2% and 5% sodium alginate, respectively) loaded with 100 mg diclofenac were also subjected to an enteric test using USP I apparatus (baskets). Both capsule formulations passed the enteric test retaining their shape (Figure 5). It should be noted, however, that the greater thickness of the proposed capsules compared with standard capsules could possibly have an impact on filling and may require modification of standard automated filling machines.

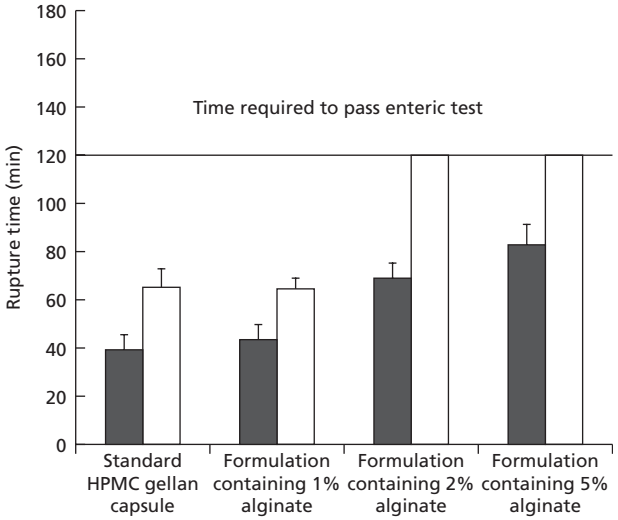

Figure 4 Average rupture time of films. Rupture in 100 mM HCl pH 1.2 for films ~ 150 μm thick (filled bars) and ~ 250 μm thick (clear bars). Results represent mean ± SD, $n = 3$.

Figure 3 Dissolution vial used for enteric film experiments showing polymer film (dyed with brilliant blue) surface to be exposed to the dissolution medium

Discussion

The rheological profile of the base material for capsule formation requires viscous behaviour at high temperatures (low values of G′ and G″) > 60°C and a gradual gelation as the temperature is lowered, resulting in G′ dominating over G″. This is illustrated clearly in formulation 2 where low

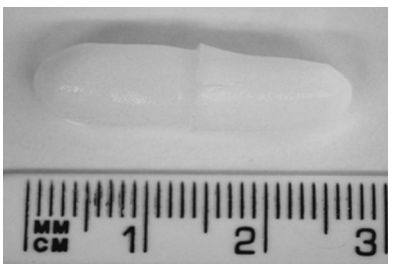

Figure 5 Capsule formed using formulation 5 (17% HPMC, 0.2% gellan gum, 2% sodium alginate) following 2 h in 100 mM HCl pH 1.2

values of G′ and G″ at 60°C are followed by swelling of HPMC particles during cooling, which caused a dramatic increase in G′ and G″ (maximum G′ value occurring at 44°C). This was followed by the formation of a gellan gel network, which provides the structure for holding the mixture on the dipping pins resulting in G′ >> G″ at 25°C. When analysed without the gellan gum present (formulation 1) the swollen HPMC particles began to dissolve at ~40°C and gave a sharp decrease in G′. Once the temperature had reached 25°C, G″ was dominating over G′ distinctive of liquids. The effect of increasing gellan gum concentration on rheology is highlighted by data collected for formulation 3 (19% HPMC, 0.2% gellan gum). Surprisingly, the gellan gum network formed was not as strong as shown in formulation 2 (19% HPMC, 0.1% gellan gum) as the HPMC began to dissolve with G′ decreasing at ~40°C, similar to HPMC alone (formulation 1). However the presence of the gellan gum provided some structure at lower temperatures, with G′ remaining close to G″ at 25°C unlike HPMC alone. This is due to the biphasic nature of the gellan gum–HPMC system;[19] the concentration of gellan gum across the whole system was very low, however the local concentration in its own phase was much higher, which allowed gelation to occur as in formulation 2 (behaviour of a similar nature has been witnessed by Lafargue *et al.*[20] in k-carrageenan starch mixtures). When the gellan gum concentration was doubled, as in formulation 3, it is postulated that the gellan gum reverts from the continuous phase to the dispersed phase preventing gelation across the whole system. Interestingly, on addition of 1% sodium alginate (formulation 4) the gellan gum gelled the system in the same manner as in formulation 2 (19% HPMC, 0.1% gellan gum), possibly due to segregative interactions between both the negatively charged sodium alginate and gellan gum causing the gellan to occupy the continuous phase. On further increase in sodium alginate concentration (replacing HPMC) (formulations 5 and 6) the gel strength of the system was gradually reduced, illustrated by reductions in G′ values at 25°C. In formulations 6 (15% HPMC, 0.2% gellan gum 5%, sodium alginate) and 7 (15% HPMC, 0.2% gellan gum, 7.5% sodium alginate) the effect of the sodium alginate concentration was evident with higher G′ and G″ (indicating increased viscosity) values at high temperature and also appeared to effect the swelling of HPMC, reducing the max G′ temperature. These results provide an insight to the behaviour of the capsule material while cooling and give an indication of the performance of the formulations when being prepared using the dip moulding process. It should be noted that the rate of cooling used for the rheological studies (1°C/min) was due to the practical necessity of accumulating data over several oscillatory cycles at each temperature. During capsule production, a first-order rate of cooling would occur with the temperature dropping from 60°C to 30°C within 1 min. This data does, however, provide an analysis of structural changes occurring during cooling and by comparing the novel formulations with a HPMC capsule formulation, we can predict whether the formulated polymer mixture has the ability to form a capsule on a dip moulding pin. To this end, consulting the rheological profile on cooling for the formulations described, formulations 4 and 5 appeared to have the most similar profile to that of a standard HPMC capsule formulation (formulation 2), and this was later confirmed using the dip moulding process.

The increase in capsule thickness on reducing dipping temperature (Figure 2), where capsule thickness ranged from 130 μm ± 0.6 μm thick when dipped at 69°C compared with dipping at 58°C which produced capsules that were 280 μm ± 2.3 μm, was due to the increase in viscosity of the capsule base material. This caused more material to be attached to the moulding pin when dipped. Moisture content values (Table 3) were slightly higher for the novel formulations than in commercial HPMC capsules (4.5%), which was likely to have been caused by the drying conditions employed in this study. The most striking results, however, were evident in the puncture force experiments. When sodium alginate was added to the system the resistance to puncture was greatly reduced to the extent that formulation 7 (containing 7.5% sodium alginate) could not be measured. This brittleness could prove problematic in large-scale capsule manufacture. There is, however, potential to plasticise the films, increasing the flexibility and therefore the resistance to puncture. This was demonstrated in a brief study by replacing 5% of the water content with the plasticiser polyethylene glycol (PEG 200), which more than doubled the puncture force resistance (data not shown). Results obtained from the enteric test (Figure 4) on films with a thickness of 150 μm revealed that only formulations 5 (17% HPMC, 0.2% gellan gum, 2% sodium alginate, 0.2% NaCl) and 6 (15% HPMC, 0.2% gellan gum, 5% sodium alginate, 0.2% NaCl) came close to the 2-h requirement. When this test was repeated with films with a thickness of 250 μm, both these formulations remained acid-insoluble for up to 2 h. Capsules prepared from formulations 5 (17% HPMC, 0.2% gellan gum, 2% sodium alginate, 0.2% NaCl) and 6 (15% HPMC, 0.2% gellan gum, 5% sodium alginate, 0.2% NaCl) filled with 100 mg diclofenac retained their shape following 2 h in 100 mM HCl (Figure 5). On examination following 2 h in acid the films and capsules were notably weak and almost gel like, and whether the harsh environment of the stomach would rupture the capsules prepared from these formulations before passage into the duodenum would require further tests such as gamma scintigraphy.[21] It has been shown previously, however, that HPMC capsules containing gellan gum as the gelling agent (rather than carrageenan) increases dissolution time in acidic conditions and in the presence of K^+ cations.[22] Therefore, it is reasonable to argue that the addition of acid-insoluble alginate to the formulation will only cause a further increase in capsule opening time. Moreover, the increased dissolution time in the presence of K^+ cations indicates that dissolution time would also be increased if the capsules were administered in the fed state. This is supported by in-vivo gamma scintigraphic studies on HPMC capsules containing gellan gum as a gelling agent,[22] where it was reported that the mean disintegration time in the fed state was 60 min compared with 28 min in the fasted state. If extrapolated to our study where resistance was achieved for 2 h in media representing the fasted state, we can predict that penetration by gastric fluid in the fed state would be prevented for at least 4 h.

Conclusions

We have created polymer film formulations that can be used to form capsule shells and that are resistant to acid for up to 2 h, providing the possibility to deliver drugs or other substances to the intestine without the need to coat the capsule or the API. The major advantages of these capsules are: no coating process is required, all materials are from non-animal origin and therefore acceptable to vegetarians and religions where consuming bovine or porcine products is not permitted. The capsules can also be prepared using a conventional dip moulding process and all materials are accepted for pharmaceutical use.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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