Drug Development and Industrial Pharmacy, 2012; 38(2): 129–157

ISSN 0363-9045 print/ISSN 1520-5762 online
DOI: 10.3109/03639045.2011.590990

informa
healthcare

REVIEW ARTICLE

Reviewing the use of ethylcellulose, methylcellulose and hypromellose in microencapsulation. Part 1: materials used to formulate microcapsules

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Abstract

This review highlights references where ethylcellulose, methylcellulose and hypromellose were used to make microcapsules. The review has been divided into three parts. This first part discusses various materials used to formulate microcapsules, such as the three encapsulating polymers as well as protective colloids, plasticizers and surfactants. The second part covers the various techniques used to make microcapsules, such as temperature-induced phase separation, emulsion solvent evaporation, solvent evaporation, film coating, and others. The third part covers the various applications for which microcapsules are used, such as modified release, improved efficacy and safety, taste- and odor-masking, and others. It is hoped that formulators can use Part 1 as a guide to the literature documenting formulation of microcapsules made from these encapsulating polymers. SciFinder was utilized to identify the pertinent literature. SciFinder leverages literature databases, such as Chemical Abstracts Service Registry and Medline. A total of 379 references were identified during the review. The need for a three-part review reflects the extensive amount of literature identified concerning these three encapsulating polymers.

Keywords: Encapsulation, microcapsule, microsphere, microparticle, multiparticulate, hydroxypropylmethylcellulose, HPMC

Introduction

The Food and Drug Administration defines microencapsulation as a process by which small, discrete solid materials, liquid droplets or gases are completely enveloped within an intact membrane[1]. Microencapsulation has been practiced for many years in printing, pharmaceutical, food, cosmetic and agricultural industries. Green and Schleicher[2] of The National Cash Register Company first disclosed the concept of microencapsulation in 1956. From Green's and Schleicher's discovery, it is apparent that microcapsules were originally designed to encapsulate inks. In fact, scientists at the National Cash Register Company obtained several pioneering patents on microencapsulated inks for printing applications[3–5].

Soon afterwards, scientists at the National Cash Register Company obtained a patent on minute polymeric capsules for drugs, in particular, using ethylcellulose to encapsulate aspirin[6]. This patent helped pioneer the utilization of microcapsules for pharmaceutical applications. Since then, over 15,000 papers and patents have been published on the topic of microencapsulation.

Microencapsulated products have found commercial success in the pharmaceutical industry. Bayer Corporation markets CIPRO Oral Suspension, which contains microcapsules consisting of ciprofloxacin, polyvinylpyrrolidone, methacrylic acid copolymer, hypromellose, magnesium stearate and polysorbate 20. The reconstituted CIPRO microcapsule formulation at a dosage of 500 mg active pharmaceutical ingredient (API) produces an equivalent blood level compared to that achieved with the CIPRO tablet, which also contains 500 mg API. Furthermore, both microcapsule suspension

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(Received 06 October 2010; revised 27 March 2011; accepted 19 May 2011)

and tablet formulations require only twice daily dosing to achieve the desired therapeutic effect[7]. The microcapsule suspension has an added benefit that the unpleasant taste of ciprofloxacin is masked[8,9].

ETHEX Corporation produces micro K EXTENCAPS capsules (formerly of A.H. Robins Company, Inc.), which contain potassium chloride (KCl) microencapsulated within an insoluble but semi-permeable ethylcellulose membrane[10,11]. The microcapsules are incorporated into a hard-gelatin capsule shell formulation. Once administered, the hard-gelatin capsule shell dissolves, and the microcapsules disperse throughout the aqueous gastrointestinal (GI) fluids. GI fluid gradually permeates the ethylcellulose barrier to gain access into the microcapsule core. Upon reaching the core, the GI fluid dissolves KCl. Dissolved KCl then permeates across the ethylcellulose barrier in modified fashion and is released over an 8–10-h time period. Modifying the release rate of KCl prevents highly localized concentrations within the GI tract and thus reduces GI irritation[10,11].

K-DUR (formerly of Key Pharmaceuticals, Inc., now of Schering-Plough Corp.) is a commercial tablet formulation containing coated KCl micropellets[12]. The KCl micropellets apparently are coated in a fluidized bed using a polymeric combination of ethylcellulose (major component) and hydroxypropylcellulose (minor component). The coated KCl micropellets are then combined with other excipients and compressed to form tablets. The tablets disintegrate rapidly upon exposure to aqueous media, and the micropellets then disperse and release KCl in modified fashion. Like micro K EXTENCAPS, the coated KCl micropellets contained in K-DUR tablets rapidly disperse following tablet disintegration. GI irritation is reduced by avoiding highly localized KCl concentrations within the GI tract[12].

Recall that over 15,000 references have been identified on the topic of microencapsulation. Hence, the microencapsulation literature was organized into various subsets in order to render it more manageable. In one subset, the literature was organized to include references where microencapsulation was achieved using ethylcellulose, methylcellulose or hypromellose. This subset consisted of 379 references and was deemed feasible to compile a comprehensive review.

References compiling this review were analyzed according to publication date (journal articles and patent applications) or issue date (granted patents), and the results of the analysis are shown in Figure 1. Utilization of ethylcellulose, methylcellulose or hypromellose for microencapsulation of pharmaceuticals has been studied since 1964, which is the year the National Cash Register Company patent (mentioned earlier) was granted[6]. Within 10 years of this original publication, almost 30 references were published. Publication frequency peaked between 1981 and 1995, when over 200 references were published. Presently, publication frequency remains high. Forty-six references were published between 1996 and 2000, and 45 references have been published since then. A high publication rate indicates that there remains significant interest in the pharmaceutical industry and in academia concerning the use of ethylcellulose, methylcellulose and hypromellose for microencapsulation.

An analysis of publications by continent is shown in Figure 2, and the top-10 countries publishing research on microencapsulation are shown in Figure 3. With the exception of Antarctica, each continent is represented to varying degrees by journal or patent publications. It is apparent that Asia, which contributed 50% of the references compiling this review, is by far the most prolific of the continents regarding publication frequency. Japan is the most prolific of the Asian countries with 72 publications, followed by India (32 publications), China

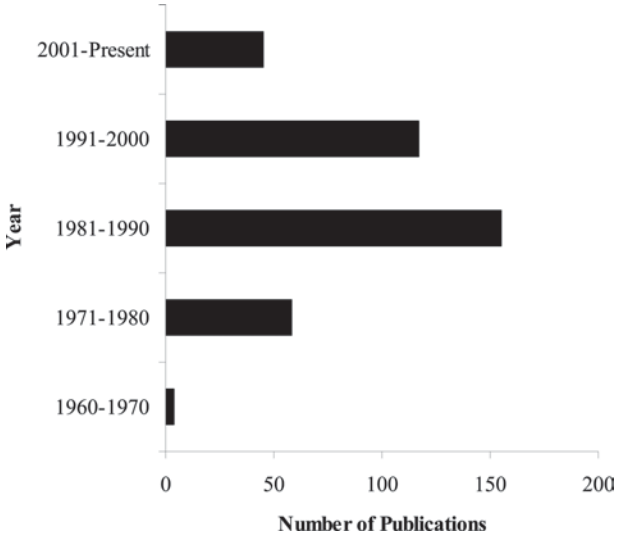

Figure 1. Analysis, by year of publication, of references compiling this literature review. The literature search was limited to references where microencapsulation had been achieved using ethylcellulose, methylcellulose or hypromellose.

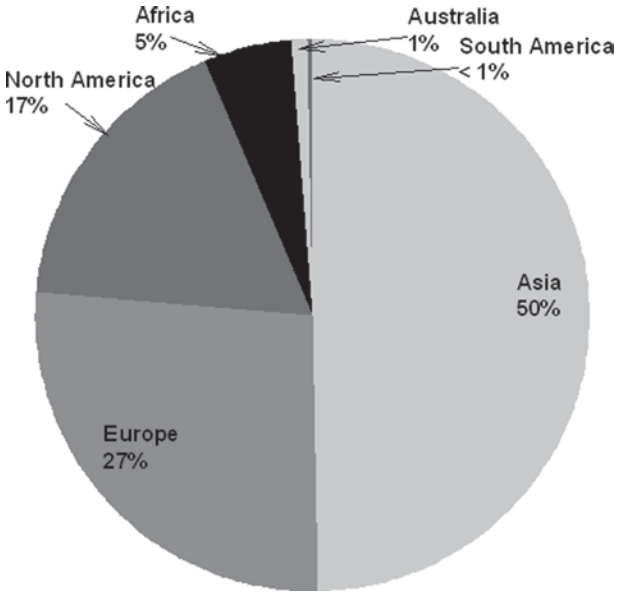

Figure 2. Analysis, by continent, of frequency of publications regarding microencapsulation.

(15 publications), Turkey (13 publications) and Taiwan (12 publications). All five of these countries are top-10 publishing countries (see Figure 3). Europe contributed 27% of the references with France (15 publications), the UK (9 publications) and Bulgaria (9 publications) being top-10 publishing countries. North America contributed 17% of the references with the USA (48 publications) being a top-10 publishing country. Africa contributed 5% of the references with Egypt (12 publications) being a top-10 publishing country, and Australia and South America contributed 1% and <1% of the references, respectively.

Upon evaluating the literature, it is evident that the pharmaceutical community lacks access to comprehensive literature reviews where ethylcellulose, methylcellulose or hypromellose have been used for microencapsulation. Only three literature reviews were identified out of the nearly 400 references compiling this review. Two reviews were published in French by Chemtob[13,14]; one review was published in Japanese by Samejima[15]; and several textbooks on the general topic of microencapsulation were identified[16–24]. Yet it remains obvious that a comprehensive review is lacking which communicates the historical impact of ethylcellulose, methylcellulose and hypromellose. Furthermore, a concise assimilation of literature has not been published regarding microencapsulation with these polymers and associated end-use applications.

The purpose of this review is to provide a comprehensive evaluation of microencapsulation with ethylcellulose, methylcellulose or hypromellose. Because of its extensive history of usage, ethylcellulose is heavily emphasized in this review as an encapsulating polymer. In fact, 372 of the 379 references discuss microencapsulation with ethylcellulose.

The review is divided into three major sections. The first section organizes journal and patent literature according to the materials utilized to achieve microencapsulation. Ethylcellulose, methylcellulose and hypromellose are discussed as encapsulating polymers; and the importance of protective colloids, plasticizers and surfactants is also discussed. The second section covers various techniques utilized to produce microcapsules, such as temperature-induced phase separation, emulsion solvent evaporation and film coating. The third section covers various end-use applications for microcapsules. That section is primarily focused on pharmaceutical applications, like modified release, enhanced efficacy and taste-masking; however, other end-use applications, like agricultural and cosmetic uses, are briefly covered as well.

Because this review is so extensive, it has been divided into three parts corresponding with the sections described above. This paper consists of Part 1, and Parts 2 and 3 will be covered in subsequent publications.

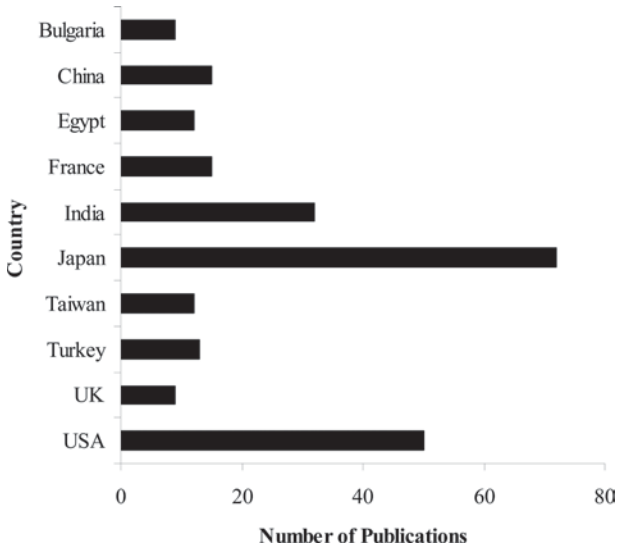

Figure 3. Analysis of the top-10 most frequently publishing countries regarding microencapsulation.

Literature search

SciFinder (Version 2007; The American Chemical Society) was utilized to identify the pertinent literature. SciFinder leverages literature databases, such as Chemical Abstracts Service Registry and Medline, to search both journal and patent literature.

The literature was searched for ethylcellulose, methylcellulose and hypromellose and then narrowed using the concepts of microcapsule and microencapsulation. The

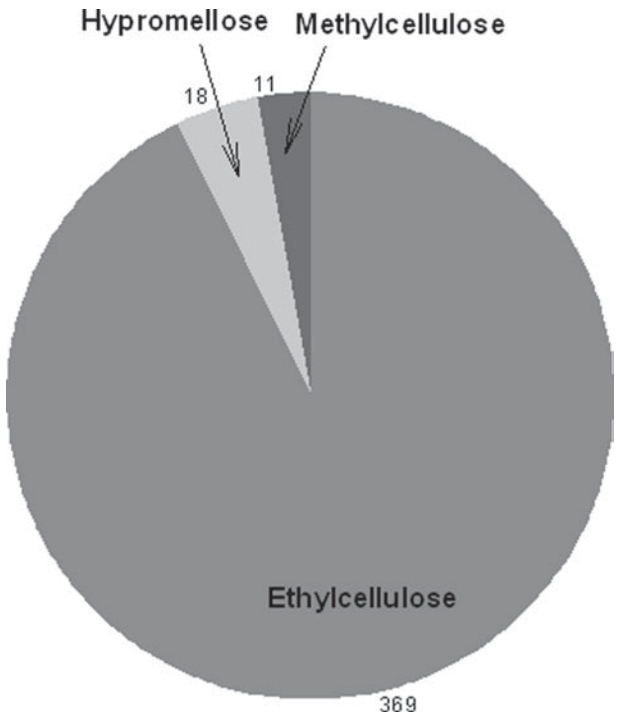

Figure 4. Analysis of the number of publications identified in this literature review by the type of encapsulating polymer. This analysis is based upon a total of 379 microencapsulation references where ethylcellulose, methylcellulose or hypromellose was used to achieve microencapsulation. Hence, more than one of these encapsulating polymers was investigated in some of the referenced studies.

resulting references were then studied to obtain the 379 references compiling this review.

Microencapsulation materials

As shown in Figure 4, it is apparent that ethylcellulose has been the most extensively used of the three encapsulating polymers. Hence, the majority of the review is dedicated to ethylcellulose. In addition to the three encapsulating polymers, the roles of protective colloids, plasticizers and surfactants are also briefly discussed.

Ethylcellulose

Ethylcellulose has been used extensively across multiple microencapsulation techniques and for various end-use applications. Table 1 lists 369 technique- and application-oriented references identified where ethylcellulose was used to produce microcapsules. Ethylcellulose often has been an encapsulating polymer of choice due to its insolubility in water. An ethylcellulose membrane typically provides a barrier through which API can be released in modified fashion into aqueous media. For example, micro K EXTENCAPS and K-DUR tablets contain KCl encapsulated within a dissolution rate-modifying ethylcellulose barrier.

An important factor to consider when formulating microcapsules is the molecular weight (MW) or standard (std) viscosity grade of ethylcellulose utilized. Table 2 lists the std viscosity grades of ethylcellulose available for pharmaceutical use. The std grade is defined by both ethoxyl substitution and the viscosity of a 5% solution of ethylcellulose in a toluene/alcohol (80/20) cosolvent mixture, which has been equilibrated to 25°C. Higher viscosity grades correspond with higher polymer MWs.

A schematic of the molecular structure of ethylcellulose is shown in Figure 5a. Anhydroglucose units make up the cellulose backbone, and the individual units can be substituted at the 2, 3 and/or 6 positions. For std grades of ethylcellulose, the degree of ethoxyl substitution ranges from 2.5 to 2.6; and this corresponds to an average ethoxyl content of 48.0–49.5% (w/w).

Utilization of ethylcellulose in modified release applications typically involves applying a rate-modifying ethylcellulose barrier to a substrate, such as a microcapsule core, powder, granule, bead or tablet. Several studies have demonstrated a correlation between ethylcellulose viscosity grade and modified release performance[25–35]. Although some of these studies have concluded otherwise[25–27,33], most have demonstrated that greater modified release is achievable with higher viscosity grades. For example, Deasy et al.[34] microencapsulated sodium salicylate within ethylcellulose of varying viscosity grades. Deasy et al. found that microcapsules of finer particle size and exhibiting slower drug release were obtained when ethylcellulose std 100 was used vs. ethylcellulose std 10. Assimopoulou and Papageorgiou[35] investigated various types of rate-modifying polymers and found that ethylcellulose provided the most suitable barrier properties for modified release of alkannin. Ethylcellulose std 10 provided microcapsules with suitable morphological

Table 1. References identified where ethylcellulose was used for microencapsulation.

Ethylcellulose references		
Abu-Izza et al., 1996[114]	Becourt et al., 2002[63]	Chemtob et al., 1989[115]
Adikwu, 1995[116]	Becourt et al., 2002[64]	Chen et al., 1994[42]
Ahlert and Evert, 1995[117]	Bergisadi and Gurvardar, 1989[118]	Chen et al., 1995[119]
Al-Omran et al., 2002[120]	Bettman et al., 1997[121]	Cheu et al., 2001[25]
Al-Omran et al., 2002[122]	Bhalerao et al., 2001[123]	Chikamatsu et al., 1984[76]
Al-Omran et al., 2002[108]	Biju et al., 2004[124]	Chow et al., 1998[125]
Alam and Eichel, 1980[126]	Bodmeier and Chen, 1989[127]	Chowdary and Rao, 1984[128]
Alam and Eichel, 1982[129]	Bodmeier and Chen, 1990[70]	Chowdary and Nageswara Rao, 1985[110]
Alpar, 1981[130]	Bodmeier and Wang, 1993[131]	Chowdary and Rao, 1985[132]
Alpar and Walters, 1981[133]	Bodmeier et al., 1995[134]	Chowdary and Rao, 1985[135]
Aly et al., 1993[136]	Bruschi et al., 2002[62]	Chowdary and Murty, 1985[137]
Amperiadou and Georgarakis, 1995[138]	Calanchi and Gentilini, 1985[94]	Chowdary and Rao, 1986[139]
Anderson, 1971[140]	Cameroni et al., 1985[141]	Chowdary and Babu, 1988[142]
Anderson et al., 1972[143]	Carpov et al., 1982[144]	Chowdhary and Ramesh, 1993[145]
Andre-Abrant et al., 2001[146]	Carpov et al., 1980[147]	Chowdary and Ratna, 1993[148]
Arabi et al., 1996[29]	Cedrati et al., 1997[149]	Chowdary and Sastry, 1997[150]
Assimopoulou and Papageorgiou, 2004[35]	Chalabala, 1984[54]	Chukwu et al., 1991[151]
Baichwal and Chidambharam, 1977[58]	Chan and Heng, 1998[28]	Cohen, 1986[152]
Baichwal and Abraham, 1980[57]	Charle et al., 1973[153]	Cordes, 1972[154]
Barik et al., 1993[155]	Chattaraj and Das, 1990[156]	Cowsar et al., 1978[157]
Barik et al., 2004[60]	Chemtob, 1984[13]	Cowsar, 1980[158]
Barzola et al., 2001[65]	Chemtob, 1987[14]	Cristallini et al., 1984[159]
Beatty, 1982[50]	Chemtob et al., 1986[160]	Curea et al., 1987[161]
Becourt et al., 2002[61]	Chemtob et al., 1986[162]	D'Onofrio et al., 1979[163]

References are listed alphabetically by the first author's or inventor's last name. Table 1 is continued in the appendix.

Table 2. Ethylcellulose grades commercially available for pharmaceutical use.

Commercial name[a]	Mfr.	Ethoxyl (%)	Viscosity range[b] (mPa-s)
ETHOCEL™ Std 4	DWC	48.0–49.5	3–5.5
ETHOCEL™ Std 7	DWC	48.0–49.5	6–8
ETHOCEL™ Std 10	DWC	48.0–49.5	9–11
ETHOCEL™ Std 14	DWC	48.0–49.5	12.6–15.4
ETHOCEL™ Std 20	DWC	48.0–49.5	18–22
ETHOCEL™ Std 45	DWC	48.0–49.5	41–49
ETHOCEL™ Std 100	DWC	48.0–49.5	90–110
Aqualon Ethylcellulose N7	Hercules	48.0–49.5	5.6–8
Aqualon Ethylcellulose N10	Hercules	48.0–49.5	8–11
Aqualon Ethylcellulose N14	Hercules	48.0–49.5	12–16
Aqualon Ethylcellulose N22	Hercules	48.0–49.5	18–24
Aqualon Ethylcellulose N50	Hercules	48.0–49.5	40–52
Aqualon Ethylcellulose N100	Hercules	48.0–49.5	80–105

Information on the commercially available grades of ethylcellulose was gathered from the ETHOCEL™ and Hercules websites, respectively.

[a]Std, standard.

[b]Viscosity of 5% solution measured at 25°C in a Ubbelohde viscometer. The cosolvent mixture is 80% toluene and 20% alcohol.

DWC, Dow Wolff Cellulosics; ™, Trademark of The Dow Chemical Company ("Dow") or an affiliated company of Dow.

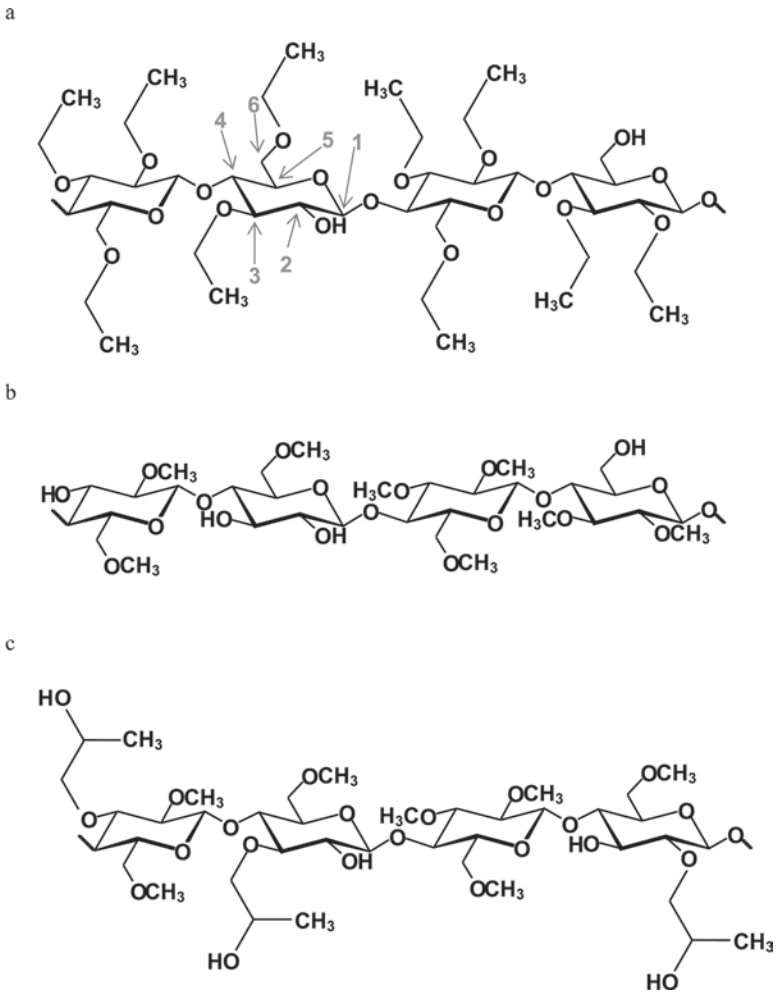

Figure 5. Schematics of the molecular structures of ethylcellulose (a), methylcellulose (b) and hypromellose (c).

properties, but the release rate of alkannin was too rapid. Ethylcellulose std 45, however, provided microcapsules with suitable morphological properties, and alkannin release was sufficiently modified.

Ethylcellulose can provide durable coatings which allow substrates to withstand impact. For example, ETHOCEL™ (Trademark of The Dow Chemical Company ("Dow") or an affiliated company of Dow) is utilized to

apply impact-resistant coatings, which protect bowling pins from damage after repeated impact[36]. Several studies have been conducted where ethylcellulose was used to produce microcapsules, which were subsequently compressed to tablets or pellets (see Table 3, which will be covered in more detail in Part 3). A number of these studies demonstrated correlation between resistance to barrier rupture during compression and the viscosity grade of ethylcellulose utilized. The K-DUR patent by Hsiao and Chou[12] (discussed earlier) specifies the preferred usage of a higher viscosity grade of ethylcellulose, like std 100, in order to reduce incidence of barrier rupture during tablet compression. Hsiao and Chou further add that a lower viscosity grade, such as std 10, could be used to formulate a rate-modifying barrier when microcapsules are not compressed (e.g. capsule formulations). Gantt et al.[37] and Venkatesh and Kramer[38] specify in separate patent applications that ethylcellulose std 100 is a preferred encapsulating polymer because it allows microencapsulated KCl crystals to retain diffusion controlling characteristics even after compression.

Some groups have published studies correlating encapsulation efficiency with viscosity grade[25,39]. Using acyclovir as model drug, Cheu et al.[25] designed a multifactorial study to investigate the effects of ethylcellulose viscosity grade, concentration and barrier:core ratio on encapsulation efficiency, stability and dissolution performance. Cheu et al. found that encapsulation efficiency was increased when a higher viscosity grade of ethylcellulose was used. Uddin et al.[39] tested a variety of microencapsulation techniques, polymers and corresponding viscosity grades to prepare microcapsules containing ascorbic acid. The purpose of encapsulating ascorbic acid was to improve its stability, modify its release and mask its acidic taste. Using the solvent evaporation technique (to be discussed in Part 2), Uddin et al. found that encapsulation efficiency was most improved by inclusion of plasticizer and use of a higher viscosity grade of ethylcellulose.

Uddin et al.[39] also found that extent of microcapsule aggregation was decreased with both the addition of polyisobutylene (PIB; a protective colloid to be discussed later) and the use of a higher viscosity grade of ethylcellulose. Before the study of Uddin et al., however, Koida et al.[40] identified a correlation between extent of microcapsule aggregation and viscosity grade of ethylcellulose. Koida et al. used PIB to reduce aggregation, but they found that aggregation could be further minimized using a higher viscosity grade of ethylcellulose.

Ethylcellulose has been used synergistically with other encapsulating polymers to achieve, for example, unique modified release performance. References were identified where ethylcellulose was used synergistically with other cellulose derivatives[41–52], glycols[53–59], acrylic acid derivatives[60–72], waxes[34,53,58,73–81], ion-exchange resins[26,27,82–89] and activated carbon[90–93].

An example of synergistic use of ethylcellulose with another cellulose derivative was published by Guyot and Fawaz[41]. Guyot and Fawaz used a solvent evaporation technique to produce microspheres containing nifedipine and ethylcellulose, nifedipine and an ethylcellulose/hydroxypropylcellulose combination or nifedipine and an ethylcellulose/hypromellose combination. Microspheres formulated using either polymer combination released nifedipine more slowly and more regularly than microspheres formulated with ethylcellulose alone. Nifedipine release from the microcapsules was best described using combined kinetics (zero- and first-order

Table 3. Application-oriented publications where microcapsules were utilized for multiparticulate compression.

Ethylcellulose references		Hypromellose references
Adikwu, 1995[116]	NL 7215117 A; Anon., 1974[164]	Ayer et al., 1994[98]
Al-Omran et al., 2002[120]	Morishita et al., 1985[165]	
Alpar, 1981[130]	Morre et al., 2002[166]	
Alpar and Walters, 1981[133]	Murav'ev and Andreeva, 1987[167]	
Ayer et al., 1994[98]	Nikolaev et al., 1990[168]	
Baichwal and Chidambharam, 1977[58]	Nikolayev and Gebre-Mariam, 1993[169]	
Baichwal and Abraham, 1980[57]	Özyazici et al., 1996[170]	
Chikamatsu et al., 1984[76]	Raghubanshi et al., 1991[171]	
Chukwu et al., 1991[151]	Sajeev et al., 2002[172]	
Curea et al., 1987[161]	Sevgi et al., 1994[173]	
Dahlström and Eriksson, 1971[174]	Shopova et al., 1987[175]	
Farid et al., 1994[176]	Singla and Nagrath, 1988[53]	
Fekete, 1992[111]	Tirkkonen and Paronen, 1993[177]	
Gantt et al., 2000[37]	Tsai and Huang, 1985[55]	
He and Hou, 1989[178]	Tuncel et al., 1996[179]	
Hosny et al., 1998[180]	Venkatesh and Kramer, 2003[38]	
Hsiao and Chou, 1989[12]	Vitkova et al., 1986[181]	
Jalsenjak et al., 1980[182]	Yazan et al., 1995[183]	
Kassem et al., 1975[184]	Zia et al., 1991[185]	
Kondo et al., 1972[186]		

No methylcellulose references were identified for this application. The references are arranged in similar format to those in Table 1.

kinetics or zero-order and Higuchi square-root kinetics). No burst effect was observed with any of the encapsulating barriers.

Baichwal and Abraham[57] and Tsai and Huang[55] published studies where ethylcellulose/polyethylene glycol combinations were used to formulate microcapsules. In both studies, ethylcellulose was formulated with varying concentrations of polyethylene glycol (PEG) 4000 to produce microcapsules for modified release. In the first study, Baichwal and Abraham found that increasing the PEG level within the ethylcellulose barrier resulted in faster metronidazole release. In addition to modifying release, microencapsulation facilitated tabletting. Tablets containing microencapsulated metronidazole were harder and less friable compared to tablets containing non-encapsulated metronidazole. In the second study, Tsai and Huang showed that modified release of indomethacin could be adjusted using ethylcellulose and varying levels of PEG during microencapsulation. Like Baichwal and Abraham, Tsai and Huang found that higher levels of PEG resulted in faster API release. Furthermore, *in vivo* animal studies demonstrated elevated and prolonged plasma levels following administration of indomethacin microencapsulated within ethylcellulose/PEG combinations. Plasma levels following administration of these microcapsules were superior to the levels achieved following administration of indomethacin microencapsulated within ethylcellulose alone.

Studies using synergistic combinations of ethylcellulose and acrylic acid derivatives were published by Bruschi et al.,[62] Becourt et al.[64] and Bodmeier and Chen[70]. Bruschi et al. developed a process to produce bi-layered microcapsules containing caffeine, which exhibited rapid release and also provided suitable taste-masking properties. The first (inner) barrier layer consisted of ethylcellulose and was applied by phase separation. The second (outer) barrier layer consisted of Eudragit E 100 and was applied via fluidized bed spray coating. The level of caffeine in the finished microcapsules was 67.5%, and the two barriers successfully masked API taste. The microcapsules, however, released 80% of encapsulated caffeine within 10 min.

Members from the same research group[64] prepared spherical agglomerates of telithromycin encapsulated within ethylcellulose and then spray-coated onto the ethylcellulose microcapsules an additional barrier layer consisting of Eudragit E 100. The final microcapsules contained 58.5% telithromycin, 6.5% ethylcellulose, 23.3% Eudragit E100 and 11.7% talc and were easily dispersed into aqueous media without agglomeration. The taste of telithromycin was successfully masked.

Bodmeier and Chen[70] produced polymeric nanosuspensions containing indomethacin using a microfluidization-solvent evaporation method. The polymeric nanoparticles exhibited both high encapsulation efficiency and reduced tendency to agglomerate. Nanoparticles containing indomethacin and ethylcellulose alone rapidly released API within 15 min. Nanoparticles designed for modified release, however, contained indomethacin and a combination of ethylcellulose and poly(methyl methacrylate) (PMMA). Ethylcellulose and PMMA formed a barrier where the two polymers functioned synergistically to modulate API release.

Ethylcellulose has been used synergistically with fatty acids and waxes for such purposes as modified release, enhanced stability and processing improvements. Baichwal and Chidambharam[58] formulated ethylcellulose microcapsules containing ascorbic acid and then applied a seal coating consisting of stearic acid or PEG to the microcapsule surface. Ascorbic acid stability was then measured under high relative humidity. The authors found that maximum stability was attained when ascorbic acid was microencapsulated within ethylcellulose and subsequently sealed with 15–30% stearic acid. Microcapsules sealed with high levels of stearic acid, however, exhibited sticking problems during tabletting. In another study, Deasy et al.[34] produced microcapsules containing sodium salicylate and ethylcellulose and furthermore applied a paraffin wax seal coating over the ethylcellulose barrier. Deasy et al. chose paraffin wax over other sealants because the paraffin wax seal coating more effectively modulated the dissolution rate of sodium salicylate. API release properties were affected by microcapsule size and the amount of seal coating applied. In yet another study, Shin and Koh[75] produced microcapsules containing methyldopa and ethylcellulose, and the microcapsules were sealed with spermaceti. Like Deasy et al., Shin and Koh found that the rate of methyldopa release could be modulated by microcapsule size and the amount of seal coating applied. Finally, Snipes and Wagner[74] produced microcapsules containing KCl, ethylcellulose and palmitic acid in order to achieve both rapid dispersion and modified release of KCl in GI media. The microcapsules, which were produced via fluidized bed spray coating, were relatively spherical (400–600 μm in diameter) and free-flowing. KCl microencapsulated within ethylcellulose alone served as the control. Ethylcellulose/palmitic acid microcapsules released KCl at a comparable rate to ethylcellulose microcapsules. Unlike the ethylcellulose microcapsules, however, ethylcellulose/palmitic acid microcapsules did not agglomerate upon addition to GI media.

Ethylcellulose has been used synergistically with ion-exchange resins and activated carbon. Ion-exchange resins and activated carbon serve similar functions in that they are substrates upon which to adsorb APIs. Moldenhauer and Nairn developed a method to produce predominantly mono-nucleated microcapsules containing theophylline and ion-exchange resins cross-linked to varying degrees (DOWEX™ 1X2, 1X4 and 1X8 resins, all from The Dow Chemical Company, Midland, MI). (DOWEX™ is a trademark of The Dow Chemical Company ("Dow") or an affiliated company of Dow.) The theophylline-ion-exchange resin cores were generated and subsequently microencapsulated

within ethylcellulose[86]. The rate of theophylline release from the microcapsules was influenced by the degree of cross-linking of the ion-exchange resin, the amount of ethylcellulose barrier applied and the smoothness of the applied ethylcellulose barrier. When ion-exchange resin with low cross-linking was used, API release appeared to follow membrane-controlled release kinetics. When ion-exchange resin with high cross-linking was used, API release appeared to follow particle diffusion-controlled release kinetics. Ishibashi et al.[92] developed microcapsules containing aspirin adsorbed onto medicinal carbon cores and encapsulated the newly formed cores within ethylcellulose. Microcapsule yield was increased using highly concentrated ethylcellulose solutions into which the aspirin-medicinal carbon cores were dispersed. API release rates were compared from the non-encapsulated aspirin-medicinal carbon cores vs. the same cores microencapsulated within ethylcellulose, and release rates were significantly more modified from the microencapsulated cores vs. the unencapsulated cores. Both adsorption of aspirin onto medicinal carbon and microencapsulation within ethylcellulose were necessary to achieve desired modified release performance.

Ethylcellulose references are organized in Tables 4–9 according to the processing techniques utilized to achieve microencapsulation. Ethylcellulose has been used as an encapsulating polymer with all of the microencapsulation techniques identified, but it has been most frequently used with temperature-induced phase separation (Table 4, 51 references). In addition, ethylcellulose has been commonly used as the encapsulating polymer for emulsion solvent evaporation (Table 5, 33 references), solution-based solvent evaporation (Table 6, 26 references), film coating (Table 7, 21 references), nonsolvent addition (Table 8, 19 references) and spray drying (Table 9, 11 references). Refer to Part 2 of the review for a more detailed explanation of microencapsulation techniques.

Regarding end-use applications, ethylcellulose has been most frequently used to achieve modified release (Table 10, 67 references). Beyond modified release, ethylcellulose has commonly been used for applications like enhanced efficacy (Table 11, 42 references), compression of microcapsules to form tablets (Table 3, 39 references), stability improvement (Table 12, 24 references) and improved safety (Table 13, 19 references). Refer to Part 3 of the review for a more detailed discussion of applications for ethylcellulose microcapsules.

Methylcellulose

In contrast to ethylcellulose, methylcellulose has not been referenced extensively. Of the 379 microencapsulation references, only 11 mentioned the use of methylcellulose. Even then, methylcellulose was either used in conjunction with other encapsulating polymers or was an alternative to a preferred encapsulating polymer, such

Table 4. Process-oriented publications where temperature-induced phase separation was utilized to make microcapsules.

Ethylcellulose references			Hypromellose references
Alam and Eichel, 1980[129]	Lin and Yang, 1986[187]	Vitkova et al., 1994[188]	Kaltsatos et al., 1989[189]
Alam and Eichel, 1982[126]	Lin and Chen, 1992[190]	Whitaker Sr., 1991[191]	
Anderson et al., 1972[143]	Miller and Anderson, 1964[6]	Wieland-Berghausen et al., 2002[192]	
Bettman et al., 1997[121]	Morse, 1971[59]		
Calanchi and Gentilini, 1985[94]	Morse and Hammes, 1974[193]		
Cameroni et al., 1985[141]	Morse et al., 1978[194]		
Carpov et al., 1980[147]	Motycka and Nairn, 1979[89]		
Carpov et al., 1982[144]	Nasa and Yadav, 1989[195]		
Chemtob et al., 1986[160]	NL 6611661; Anon., 1967[196]		
Chemtob et al., 1986[162]	Nixon and Wong, 1990[197]		
Deasy et al., 1980[34]	Powell, 1993[198]		
Doshi et al., 1994[199]	Rak et al., 1984[200]		
el-Helw, 1987[201]	Safwat and El-Shanawany, 1989[71]		
Fan et al., 1996[202]	Samejima et al., 1982[106]		
Fekete et al., 1989[112]	Samejima et al., 1985[47,48]		
Friend et al., 1997[203]	Samejima et al., 1983[80]		
Inoe, 1992[204]	Shin and Koh, 1989[75]		
John, 1979[205]	Singh and Robinson, 1988[113]		
Kaltsatos et al., 1989[189]	Singh and Robinson, 1990[30]		
Kato, 1981[79]	Sveinsson and Kristmundsdottir, 1992[206]		
Koida et al., 1983[40]	Szretter and Zakrzewski, 1984[207]		
Koida et al., 1986[208]	Uddin et al., 2001[39]		
Kristl et al., 1991[209]	Vitkova et al., 1983[56]		
Lin, 1985[210]	Vitkova et al., 1984[211]		

No methylcellulose references were identified where temperature-induced phase separation was used. The references are arranged in similar format to those in Table 1.

Table 5. Process-oriented publications where emulsion solvent evaporation was utilized to make microcapsules.

Ethylcellulose references		Hypromellose references
Abu-Izza et al., 1996[114]	Morishita et al., 1981[212]	Guyot and Fawaz, 1998[41]
Amperiadou and Georgarakis, 1995[138]	Mortada, 1982[213]	
Bhalerao et al., 2001[123]	Murthy and Chowdary, 2004[96]	
Bodmeier and Chen, 1989[127]	Murthy and Chowdary, 2005[214]	
Bodmeier and Chen, 1990[70]	Perez-Martinez et al., 2001[215]	
Cheu et al., 2001[25]	Ravichandran et al., 2001[216]	
Das, 1991[217]	Ruiz et al., 1990[218]	
Elbahri and Taverdet, 2005[219]	Sheorey et al., 1991[220]	
Goto et al., 1985[32]	Sriwongjanya and Bodmeier, 1997[82]	
Guyot and Fawaz, 1998[41]	Uno et al., 1984[221]	
Huang and Ghebre-Sellassie, 1989[222]	Wieland-Berghausen et al., 2002[192]	
Jones and Pearce, 1995[223]	Yang et al., 2000[224]	
Kentepozidou and Kiparissides, 1995[225]	Yang et al., 2001[226]	
Kiritani, 1973[227]	Yang et al., 2001[228]	
Lin and Wu, 1999[229]	Yang et al., 2005[230]	
Morishita et al., 1973[231]	Zandi et al., 1998[232]	
Morishita et al., 1976[233]		

No methylcellulose references were identified where emulsion solvent evaporation was used. The references are arranged in similar format to those in Table 1.

Table 6. Process-oriented publications where solvent evaporation was utilized to make microcapsules.

Ethylcellulose references	
Andre-Abrant et al., 2001[146]	Manekar et al., 1992[234]
Arabi et al., 1996[29]	Manekar et al., 1993[235]
Assimopoulou and Papageorgiou, 2004[35]	Moldenhauer and Nairn, 1991[85]
Cristallini et al., 1984[159]	Moldenhauer and Nairn, 1992[84]
Dubernet et al., 1991[236]	Moldenhauer and Nairn, 1994[83]
Elbary et al., 2001[66]	Rhee et al., 1997[67]
Ghorab et al., 1990[237]	Sarin et al., 1985[49]
Ibrahim et al., 1990[238]	Tsujiyama et al., 1989[46]
Khalil and El-Gamal, 1973[239]	Uchida et al., 1987[240]
Kosenko et al., 1986[241]	Uchida et al., 1992[44]
Kristmundsdottir and Ingvarsdottir, 1994[242]	Uddin et al., 2001[39]
Ku and Kang, 1991[243]	Yoshida, 1972[244]
Manekar et al., 1992[245]	Zhu et al., 1992[246]

No methylcellulose or hypromellose references were identified where solvent evaporation was used. The references are arranged in similar format to those in Table 1.

Table 7. Process-oriented publications where film coating was utilized to make microcapsules.

Ethylcellulose references	Methylcellulose references	Hypromellose references
Becourt et al., 2002[61]	Zulkarnain, 1996[247]	Zulkarnain, 1996[247]
Becourt et al., 2002[64]		
Bruschi et al., 2002[62]		
Calanchi and Gentilini, 1985[94]		
Cordes, 1972[154]		
Elbary et al., 2001[66]		
Fukumori et al., 1991[248]		
Fukumori et al., 1991[249]		
Giannini and Bashour, 1989[97]		
Han and Li, 2001[250]		
Ichikawa and Fukumori, 2000[72]		
Kassem et al., 1978[81]		
Kim et al., 1999[251]		
Knezevic et al., 1998[252]		
Lippold et al., 1989[109]		
Persson and Lindblom, 1981[253]		
Rhee et al., 1997[67]		
Senjkovic and Jalsenjak, 1984[254]		
Snipes and Wagner, 1989[74]		
Wieland-Berghausen et al., 2002[192]		
Zulkarnain, 1996[247]		

The references are arranged in similar format to those in Table 1.

as ethylcellulose. Refer to Table 14 for the methylcellulose references.

Calanchi and Gentilini[94] formulated granules containing a highly water-soluble API, such as metoclopramide hydrochloride, and a hydrocolloid, such as methylcellulose or hypromellose; and the granules were subsequently microencapsulated within ethylcellulose via coacervation or fluidized bed spray coating. The hydrocolloid and ethylcellulose barrier functioned synergistically to modify release of the highly soluble API for at least 12 h. Although either methylcellulose or hypromellose could be used as hydrocolloid, hypromellose was more frequently used in the patent examples.

Besides the work of Calanchi and Gentilini, a patent by Fuji Photo Film Co., Ltd. was the only other reference identified where methylcellulose was used as a primary ingredient for microencapsulation (1983). In the Fuji patent, ink toner was microencapsulated for printing applications. An oil-in-water (o/w) emulsion was formulated,

and methylcellulose was used to stabilize the emulsified oil phase. The emulsified droplets were eventually solidified, yielding a dry powder consisting of microencapsulated ink toner.

Golzi et al.[95] produced ethylcellulose microcapsules to modify release and/or mask API taste. The microcapsules contained API and additives dispersed throughout the ethylcellulose barrier. Ethylcellulose was dissolved in cyclohexane, and the API and additives were subsequently dispersed, rather than dissolved, into the polymer solution. The presence of methylcellulose as additive modulated such properties as barrier permeability, mechanical resistance, plasticity and aesthetics (color, odor or taste).

Table 8. Process-oriented publications where nonsolvent addition was utilized to make microcapsules.

Ethylcellulose references	
Al-Omran et al., 2002[108]	Motycka and Nairn, 1979[89]
Barik et al., 1993[155]	Nixon and Meleka, 1984[255]
Barik et al., 2004[60]	Nixon and Nimmannit, 1985[256]
D'Onofrio et al., 1979[163]	Nixon and Wong, 1990[197]
El-Helw and Bayomi, 2000[257]	Salib et al., 1976[258]
Itoh et al., 1980[259]	Wu et al., 1993[260]
Khalil and El-Gamal, 1973[239]	Wu et al., 1994[43]
Khanna et al., 1982[77]	Yazici et al., 1996[261]
Moldenhauer and Nairn, 1992[84]	Zhang et al., 2000[26,27]
Moldenhauer and Nairn, 1994[83]	

No methylcellulose or hypromellose references were identified where nonsolvent addition was used. The references are arranged in similar format to those in Table 1.

Why is methylcellulose a less frequently referenced polymer in microencapsulation compared to ethylcellulose? Unlike ethylcellulose, methylcellulose is a hydrophilic, water-soluble cellulose ether. Methylcellulose, when used as encapsulating polymer, is unable to provide modified release performance to the same extent as ethylcellulose. When methylcellulose microcapsules are added to water, the thin methylcellulose membranes

Table 9. Process-oriented publications where spray drying was utilized to make microcapsules.

Ethylcellulose references	Methylcellulose references	Hypromellose references
Forni et al., 1991[262]	Du et al., 2001[263]	Lin et al., 2004[264]
JP 58035111 A2; Anon., 1981[265]		Du et al., 2001[263]
Kitakoji et al., 1973[266]		Wan et al., 1992[99]
Liao et al., 2003[267]		
Lin et al., 2004[264]		
Mao and Zhang, 1994[268]		
Sfar and Karoui, 1989[73]		
Uddin et al., 2001[39]		
Vo et al., 2000[269]		
Yamada et al., 1996[270]		
Zhang et al., 2000[26,27]		

The references are arranged in similar format to those in Table 1.

Table 10. Application-oriented publications where microcapsules were utilized to achieve modified release.

Ethylcellulose references		
Adikwu, 1995[116]	Hsiao and Chou, 1989[12]	Rak et al., 1984[271]
Alpar, 1981[130]	Hu et al., 1999[272]	Rani et al., 1994[273]
Alpar and Walters, 1981[133]	Ishibashi et al., 1985[91]	Sajeev et al., 2002[172]
Ayer et al., 1994[98]	Jalsenjak et al., 1980[182]	Samejima et al., 1985[47,48]
Baichwal and Abraham, 1980[57]	Karakasa et al., 1994[274]	Sevgi et al., 1994[173]
Bergisadi and Gurvardar, 1989[118]	Kato, 1981[275]	Shindo, 1988[276]
Biju et al., 2004[124]	Kato and Nemoto, 1978[277]	Shopova et al., 1987[175]
Chukwu et al., 1991[151]	Kato et al., 1979[278]	Tanaka, 1978[279]
Cohen, 1986[152]	Kimura et al., 1999[280]	Tsai and Huang, 1985[55]
Curea et al., 1987[161]	Kondo et al., 1972[186]	Tsujiyama et al., 1990[45]
Dailey and Dowler, 1995[281]	Kozlova et al., 1977[282]	Uchida and Goto, 1988[283]
Deshpande and Njikam, 1977[284]	Lavasanifar et al., 1997[285]	Uchida et al., 1989[286]
Ducroux et al., 1984[287]	Lee et al., 1984[33]	Utsuki et al., 1996[288]
Echigo et al., 1982[289]	Lin et al., 1988[290]	Venkatesh and Kramer, 2003[38]
Fernandez-Urrusuno et al., 2000[291]	Lippmann et al., 1981[11]	Vitkova et al., 1986[181]
Gantt et al., 2000[37]	Maysinger and Jalsenjak, 1983[292]	Yalabik-Kas, 1983[293]
Georgiev et al., 1994[69]	Morre et al., 2002[166]	Yazan et al., 1995[183]
Gold, 2001[294]	Murav'ev and Andreeva, 1987[167]	Yokota et al., 1994[90]
Golzi et al., 2004[95]	Nikolayev and Gebre-Mariam, 1993[169]	Zia et al., 1991[185]
Goto, 1994[295]	Okamoto et al., 1986[296]	
Goto et al., 1973[297]	Özyazici et al., 1996[170]	
Guo and Xu, 1998[298]	Portnyagina et al., 1991[299]	
He and Hou, 1989[178]	Putcha et al., 2005[300]	
Hosny et al., 1998[180]	Raghubanshi et al., 1991[171]	

The references are arranged in similar format to those in Table 1. Table 10 is continued in the appendix.

Table 11. Application-oriented publications where microcapsules were utilized to enhance efficacy.

Ethylcellulose references		Hypromellose references
Ayer et al., 1994[98]	Morishita et al., 1985[165]	Ayer et al., 1994[98]
Barzola et al., 2001[65]	Murgu et al., 1981[301]	Hasçiçek et al., 2003[100]
Beatty, 1982[50]	Nemoto and Kato, 1981[302]	
Biju et al., 2004[124]	Nemoto and Kato, 1984[303]	
Curea et al., 1987[161]	Nikolayev and Gebre-Mariam, 1993[169]	
Dahlström and Eriksson, 1971[174]	Okamoto et al., 1986[296]	
Dailey and Dowler, 1995[281]	Palomo et al., 1996[304]	
Dailey and Dowler, 1996[305]	Portnyagina et al., 1991[299]	
Echigo et al., 1982[289]	Rak et al., 1984[271]	
Eley et al., 1992[306]	Shindo, 1988[276]	
Guo and Xu, 1998[298]	Takada, 2000[307]	
Hu et al., 1999[272]	Tsai and Huang, 1985[55]	
Jouffroy, 1984[308]	Tsujiyama et al., 1990[45]	
Karakasa et al., 1994[274]	Tuncel et al., 1996[179]	
Kato, 1981[275]	Uchida et al., 1989[286]	
Kato and Nemoto, 1978[277]	Utsuki et al., 1996[288]	
Kato et al., 1979[278]	Wang et al., 1993[309]	
Kato et al., 1985[310]	Wang et al., 1993[311]	
Kimura et al., 1999[280]	Wang et al., 1995[312]	
Lin et al., 1988[290]	Wang et al., 1996[313]	
Matsumoto and Ugajin, 1989[314]	Zhang et al., 1993[315]	

No references were identified where methylcellulose microcapsules were used to enhance efficacy. The references are arranged in similar format to those in Table 1.

Table 12. Application-oriented publications where microcapsules were utilized to improve stability.

Ethylcellulose references		Hypromellose references
Anderson, 1971[140]	NL 7215117 A; Anon., 1974[164]	Ayer et al., 1994[98]
Ayer et al., 1994[98]	Morishita et al., 1985[165]	
Baichwal and Chidambharam, 1977[58]	Morse and Hammes, 1972[316]	
Beatty, 1982[50]	Palomo et al., 1996[304]	
Cedrati et al., 1997[149]	Rani et al., 1994[273]	
Cowsar et al., 1978[157]	Sajeev et al., 2002[172]	
Goto et al., 1973[297]	Sakuma and Atsumi, 1990[317]	
Harte, 1978[318]	Singla and Nagrath, 1988[53]	
Heintz and Teipel, 2000[319]	Szretter and Zakrzewski, 1987[320]	
Kallstrand et al., 1986[321]	Wang et al., 1995[312]	
Kantor et al., 1989[322]	Wang et al., 1996[313]	
Kassem et al., 1975[184]	Yokoyama and Shibata, 1987[323]	

No references were identified where methylcellulose microcapsules were used to improve stability. The references are arranged in similar format to those in Table 1.

rapidly hydrate. Dissolution of methylcellulose follows, leaving the microcapsule cores without rate-modifying barriers.

A schematic of the molecular structure of methylcellulose is shown in Figure 5b. Methylcellulose is methoxylated at the 2, 3 and/or 6 positions of the anhydroglucose units. The degree of methoxyl substitution ranges from 1.6 to 1.9, which corresponds to an average substitution level of 27.5–31.5% (w/w).

Microencapsulation is frequently executed in either an organic solution or an emulsion system containing organic solvent, and the encapsulating polymer is typically dissolved within the solvent. In contrast to ethylcellulose, there are few organic solvent or cosolvent choices for methylcellulose. Cosolvent systems able to dissolve methylcellulose may require the presence of highly regulated or harmful solvents, like methylene chloride. In contrast, ethylcellulose can be easily dissolved in relatively nontoxic solvents, like ethanol or ethyl acetate[52,84,96]. Lack of solvent choices limits feasibility of producing methylcellulose microcapsules.

Hypromellose

A schematic of the molecular structure of hypromellose is shown in Figure 5c. Hypromellose is either methoxylated or hydroxypropoxylated at the 2, 3 and/or 6 positions of the anhydroglucose units. The degree of methoxyl substitution ranges from 1.2 to 2.0, which corresponds to an average substitution level ranging from 19.0 to 30.0% (w/w). The degree of hydroxypropoxyl substitution

Table 13. Application-oriented publications where microcapsules were utilized to reduce toxicity.

Ethylcellulose references	Methylcellulose references
Barzola et al., 2001[65]	Cohen, 1986[152]
Bergisadi and Gurvardar, 1989[118]	
Biju et al., 2004[124]	
Cohen, 1986[152]	
Dahlström and Eriksson, 1971[174]	
Dailey and Dowler, 1995[281]	
Eley et al., 1992[306]	
Fernandez-Urrusuno et al., 2000[291]	
Hsiao and Chou, 1989[12]	
Kato and Nemoto, 1978[277]	
Lavasanifar et al., 1997[285]	
Lee et al., 1984[33]	
Lippmann et al., 1981[11]	
Murgu et al., 1981[301]	
Nemoto and Kato, 1984[303]	
Okamoto et al., 1986[296]	
Putcha et al., 2005[300]	
Shindo, 1988[276]	
Vitkova et al., 1986[181]	

No references were identified where hypromellose microcapsules were used to reduce toxicity. The references are arranged in similar format to those in Table 1.

Table 14. References identified where methylcellulose or hypromellose was used for microencapsulation.

Methylcellulose references	Hypromellose references
Calanchi and Gentilini, 1985[94]	Ayer et al., 1994[98]
Chowdary and Ratna, 1993[148]	Calanchi and Gentilini, 1985[94]
Cohen, 1986[152]	Du et al., 2001[263]
Du et al., 2001[263]	Gantt et al., 2000[37]
Katsumi, 1983[324]	Giannini and Bashour, 1989[97]
Gantt et al., 2000[37]	Gold, 2001[294]
Golzi et al., 2004[95]	Golzi et al., 2004[95]
Jones and Pearce, 1995[223]	Guyot and Fawaz, 1998[41]
Lin et al., 2004[264]	Hasçiçek et al., 2003[100]
Venkatesh and Kramer, 2003[38]	Kaltsatos et al., 1989[189]
Zulkarnain, 1996[247]	Lin et al., 2004[264]
	Morishita et al., 1985[165]
	Pöllinger et al., 1997[8]
	Pöllinger et al., 1999[325]
	Pöllinger et al., 2000[9]
	Venkatesh and Kramer, 2003[38]
	Wan et al., 1992[99]
	Zulkarnain, 1996[247]

The references are arranged in similar format to those in Table 1.

ranges from 0.1 to 0.3, which corresponds to an average substitution level ranging from 4.0 to 12.0%. There are various viscosity grades and chemistries of hypromellose, depending upon MW, methoxyl and hydroxypropoxyl contents, as outlined in Tables 15 and16.

Like methylcellulose, hypromellose has not been as commonly referenced as ethylcellulose to formulate microcapsules. Hypromellose has, however, been referenced to a greater extent than methylcellulose (see Table 14). In fact, hypromellose is present as a synergistic encapsulating polymer in CIPRO Oral Suspension.

The Orange Book patents for CIPRO Oral Suspension reveal that ciprofloxacin is microencapsulated within a mixture of Eudragit NE 30D and hypromellose in order to mask the unpleasant taste of ciprofloxacin without hindering its release in either strongly or weakly acidic media[8,9]. The combination of Eudragit NE 30 D and hypromellose provides optimal taste-masking followed immediately by rapid API release at pH 1 and 4.5. Microencapsulation is achieved via fluidized bed spray coating using a Wurster insert. Eudragit NE 30D provides the insoluble portion of the coating. Hypromellose, which serves as the pore-forming component, quickly dissolves following oral administration and allows gastric media to rapidly penetrate the barrier and dissolve ciprofloxacin for subsequent release. A low-viscosity hypromellose grade equivalent to METHOCEL™ E3PLV (see Tables 15) is used in the patent examples. (METHOCEL™ is a trademark of The Dow Chemical Company ("Dow") or an affiliated company of Dow.) Most preferably, a combination of Eudragit NE 30D and hypromellose is used at a ratio of 100:40.

As discussed earlier, Calanchi and Gentilini[94] granulated a highly water-soluble API together with a hydrocolloid, preferably hypromellose, followed by microencapsulation of the granules within ethylcellulose. The presence of hypromellose in the microcapsule core enabled matrix-type modified release via polymeric swelling upon contact with dissolution media. The matrix-type modified release imparted by hypromellose coupled with the barrier-type modified release imparted by ethylcellulose synergistically modified release of highly water-soluble APIs, such as metoclopramide HCl.

In another example, Gantt et al.[37] formulated microcapsules containing KCl, where ethylcellulose was used as the encapsulating polymer to achieve modified release. The ethylcellulose barrier was applied via coacervation (see discussion of coacervation in Part 2). After the ethylcellulose barrier was applied, an outer layer consisting of hypromellose and PEG was applied via fluidized bed spray coating. The hypromellose/PEG layer served as an enhanced tablet binder and to minimize rupture of the underlying ethylcellulose barrier during compression. The hypromellose/PEG layer served as an enhanced binder because a minimal amount of this binder was necessary to facilitate suitable tablet hardness. In addition, the hypromellose/PEG layer allowed the use of lower compaction pressure, which also helped minimize rupture of the rate-modifying ethylcellulose barrier.

Similarly, Venkatesh and Kramer[38] developed microcapsules containing KCl where ethylcellulose was used as the encapsulating polymer. Following coacervation of the rate-modifying ethylcellulose barrier, an outer layer consisting of hypromellose and PEG was applied to the microcapsules to protect the underlying ethylcellulose

Table 15. Dow Wolff Cellulosics' commercially available methylcellulose and hypromellose grades.

Commercial name[a]	Mfr.	Chemistry type[b]	MO[c] (%)	HPO[d] (%)	Viscosity range
METHOCEL™ A15PLV	DWC+	MC	27.5–31.5	0	12–18[e]
METHOCEL™ A4CP	DWC+	MC	27.5–31.5	0	300–560[e]
METHOCEL™ A15CP	DWC+	MC	27.5–31.5	0	1125–2100[e]
METHOCEL™ A4MP	DWC+	MC	27.5–31.5	0	3000–5600[e]
METHOCEL™ E3PLV	DWC+	HPMC 2910	28–30	7–12	2.4–3.6[f]
METHOCEL™ E5PLV	DWC+	HPMC 2910	28–30	7–12	4–6[f]
METHOCEL™ E6PLV	DWC+	HPMC 2910	28–30	7–12	4.8–7.2[f]
METHOCEL™ E15PLV	DWC+	HPMC 2910	28–30	7–12	12–18[f]
METHOCEL™ E50PLV	DWC+	HPMC 2910	28–30	7–12	40–60[f]
METHOCEL™ E4MP	DWC+	HPMC 2910	28–30	7–12	2663–4970[f]
METHOCEL™ E10MP CR	DWC+	HPMC 2910	28–30	7–12	9525–17,780[f]
METHOCEL™ F4PLV	DWC+	HPMC 2906	27–30	4–7.5	3.7–5.3[f]
METHOCEL™ F50P	DWC+	HPMC 2906	27–30	4–7.5	40–60[f]
METHOCEL™ F4MP	DWC+	HPMC 2906	27–30	4–7.5	2663–4970[f]
METHOCEL™ K3PLV	DWC+	HPMC 2208	19–24	7–12	2.4–3.6[f]
METHOCEL™ K100PLV	DWC+	HPMC 2208	19–24	7–12	80–120[f]
METHOCEL™ K4MP	DWC+	HPMC 2208	19–24	7–12	2663–4970[f]
METHOCEL™ K15MP	DWC+	HPMC 2208	19–24	7–12	13,275–24,780[f]
METHOCEL™ K100MP	DWC+	HPMC 2208	19–24	7–12	75,000–140,000[f]

Information was gathered from the METHOCEL™ website.
[a]A, A chemistry; E, E chemistry; F, F chemistry; K, K chemistry; C, previous number × 10^2; M, previous number × 10^3; P, premium; LV, low viscosity; CR, controlled release.
[b]MC = methylcellulose; HPMC = hypromellose.
[c]MO = methoxyl substitution.
[d]HPO = hydroxypropoxyl substitution.
[e]Viscosity ranges reported for METHOCEL A chemistry grades are measured according to the USP 32 / NF 27 test method. The solvent is water. The unit of measure is cP.
[f]Viscosity ranges reported for METHOCEL E, F and K chemistry grades are measured according to harmonized pharmacopeial test methods (Harmonized: European, Japanese and US Pharmacopeias). The unit of measure is mPa-s. When the viscosity of a 2% solution is less than 600 mPa-s, viscosity is measured at 20 °C using a Ubbelohde viscometer. When the viscosity of a 2% solution is greater than 600 mPa-s, viscosity is measured at 20 °C using a Brookfield viscometer.
™: Trademark of The Dow Chemical Company ("Dow") or an affiliated company of Dow.
+: Dow Wolff Cellulosics.

Table 16. Hercules' commercially available methylcellulose and hypromellose grades.

Commercial name[α]	Mfr.	Chemistry type[β]	Nominal viscosity (cP)
Benecel methylcellulose A15C PH	Hercules	MC	1500
Benecel methylcellulose A4M PH	Hercules	MC	4000
Benecel hypromellose E3PH	Hercules	HPMC 2910	3
Benecel hypromellose E5PH	Hercules	HPMC 2910	5
Benecel hypromellose E6PH	Hercules	HPMC 2910	6
Benecel hypromellose E15 PH	Hercules	HPMC 2910	15
Benecel hypromellose E50 PH	Hercules	HPMC 2910	50
Benecel hypromellose E4M PH	Hercules	HPMC 2910	3600
Benecel hypromellose E10M PH	Hercules	HPMC 2910	10,000
Benecel hypromellose K100LV PH	Hercules	HPMC 2208	100
Benecel hypromellose K4M PH	Hercules	HPMC 2208	3600
Benecel hypromellose K15M PH	Hercules	HPMC 2208	18,000
Benecel hypromellose K35M PH	Hercules	HPMC 2208	35,000
Benecel hypromellose K100M PH	Hercules	HPMC 2208	100,000
Benecel hypromellose K200M PH	Hercules	HPMC 2208	200,000

Information was gathered from the Hercules website.
α: A = A chemistry; E = E chemistry; K = K chemistry; C = previous number X 10^2; M = previous number X 10^3; LV = low viscosity.
β: MC = methylcellulose; HPMC = hypromellose.

barrier from rupturing during tablet compression. The tablets would then disintegrate upon introduction into aqueous media to reveal the original microcapsules. The microcapsules would disperse over a broad area within the GI tract, release KCl in modified fashion and reduce incidence of localized GI irritation from KCl.

In yet another example, hypromellose was used as a binder rather than an encapsulating polymer[97]. A mixture of amoxicillin and hypromellose was layered onto sucrose nonpareil cores. Hypromellose served to bind the API to the core surface. A taste-masking layer consisting of ethylcellulose and PEG was then applied to encapsulate the API. The microencapsulated API was then metered into unit-dose packets or further formulated into capsules or tablets. Hence, hypromellose served a critical role in formulating microcapsules but did not serve as the encapsulating polymer.

As previously described, Guyot and Fawaz[41] used either hypromellose or hydroxypropylcellulose synergistically with ethylcellulose to formulate microcapsules for modified release. The synergistic combinations of polymers improved encapsulation efficiency and more effectively modified API release. In fact, microcapsules formulated with synergistic combinations exhibited slower, more regular API release than those encapsulated within ethylcellulose alone. This was a surprising finding given the fact that hypromellose and hydroxypropylcellulose are both hydrophilic polymers, which are often used as pore formers to facilitate API release across rate-modifying polymeric barriers.

Some references were identified where hypromellose was employed as the primary encapsulating polymer. For example, Ayer et al.[98] patented a formulation where sodium valproate was coated with polyethylene oxide (PEO) in a fluidized bed spray coater. The coated API was then microencapsulated within hypromellose in order to protect the underlying hygroscopic API from moisture. Microencapsulation within hypromellose also prepared the hygroscopic API for further downstream processing, such as tabletting and tablet coating.

Wan et al.[99] spray dried an API in conjunction with hypromellose and various plasticizers in order to study the effect of plasticizer on the properties of the resulting microcapsules. Although Wan et al. used hypromellose as the encapsulating polymer, the focus of the paper was on microcapsule properties as a function of plasticizer. This reference will be discussed in greater detail in the section about plasticizers.

Like Wan et al., Hasçiçek et al.[100] produced microspheres via spray drying using hypromellose as the encapsulating polymer. The microspheres were intended for intranasal delivery, and hypromellose was chosen as the encapsulating polymer due to its mucoadhesive properties. An encapsulating polymer with mucoadhesive properties was needed in order to enhance API retention within the nasal cavity. Enhanced retention was necessary to improve absorption of gentamicin sulfate, a polar API, across the lipophilic nasal epithelium. Upon contacting the moist mucosal layer lining the epithelium, hypromellose would hydrate and swell. The hydrated hypromellose gel layer would adhere the microspheres to the nasal mucosa and facilitate API dissolution and absorption across the epithelium.

Protective colloids

Protective colloids are often used during microencapsulation in order to induce polymer coacervation and to reduce the tendency of microcapsules to agglomerate during formation[39,75,83,86,101–106]. Table 17 lists references identified where protective colloids were used during microencapsulation. Analyses of the usage frequency of protective colloids are shown in Figures 6 and 7. Figure 6 shows the total usage of each type of protective colloid. A total of 79 references were identified where protective colloids were used during microencapsulation. The two most commonly used protective colloids are polyethylene (PE) and PIB. Figure 7 shows usage frequencies of protective colloids with some of the most commonly employed microencapsulation techniques (discussed in Part 2).

From Figure 7, protective colloids apparently are most frequently employed with temperature-induced phase separation. Twenty-one references were identified where PE was used as the protective colloid. PIB was used in 15 of the references. Beyond these two protective colloids, butyl rubber (4 refs.), ethylene vinyl acetate (4 refs.), paraffin (2 refs.) and silicone (1 ref.) served as protective colloids during microencapsulation via temperature-induced phase separation. To be concise, one reference for PE and one for PIB will be discussed.

Powell and Anderson[107] used PE as a coacervation-inducing agent. In one of their examples, Powell and Anderson first prepared an encapsulating system consisting of cyclohexane (2000 g), PE (40 g), ethylcellulose std 100 (40 g) and acetylated monoglyceride (40 g). They used PE with a MW and ball-and-ring softening point of 7000 and 100-1° (determined by ASTM D-36-62), respectively. The core phase was then prepared by first dissolving saccharose (270 g) and gum Arabic (27 g) into hot water (81 g). Milled amobarbital (148 g, <150 μm) was dispersed into the aqueous solution after it was equilibrated to 70°C. The newly formed aqueous dispersion was added to the heated (70°C) encapsulating system described above to form dispersed droplets with diameters ranging from 200 to 1000 μm. Water from the internal phase was removed using anhydrous silicone dioxide gel (220 g, particle size <420 μm). After 4 h, the microcapsules were isolated via filtration.

Koida et al.[103] studied the effect of varying MW of PIB on the properties of ethylcellulose microcapsules. Use of higher MW grades of PIB reduced the incidence of microcapsule aggregation. In fact, microcapsule aggregation was almost completely prevented using PIB with a MW greater than 6×10^5. The MW of PIB also influenced the release rate of microencapsulated API. Release rate was minimized when PIB with a MW of 2×10^5 was employed. Koida et al. also investigated the effects of MW combinations of PIB on release rate. They found that release rate was further minimized when a MW combination of 9.5×10^5 and 3×10^4 was employed at a weight ratio of 1:4. Higher proportions of low MW PIB resulted in increased wall thickness and compactness but lower

Table 17. References identified where protective colloids were utilized to make microcapsules.

Protective colloid	References	
Butyl rubber	Alam and Eichel, 1982[126]	Miller and Anderson, 1964[6]
	Alam and Eichel, 1980[129]	Samejima et al., 1982[106]
	Hirata and Niki, 1975[326]	
Ethylene vinyl acetate	Friend et al., 1997[203]	Lin and Yang, 1986[187]
	Lin, 1985[210]	Lin et al., 1988[290]
	Lin et al., 1985[104]	Lin and Chen, 1992[190]
Gelatin	Yang et al., 2001[228]	
Paraffin	Dobetti et al., 1999[327]	Samejima et al., 1985[47,48]
	Motycka and Nairn, 1979[89]	Wieland-Berghausen et al., 2002[192]
Polybutadiene	Das, 1993[328]	
Polyethylene	Bettman et al., 1997[121]	Kondo and Ueda, 1973[329]
	Calanchi and Gentilini, 1985[94]	NL 7215117 A; Anon., 1974[164]
	Carpov et al., 1980[147]	Morse, 1971[59]
	Charle et al., 1973[153]	Morse and Hammes, 1974[193]
	Fan et al., 1996[202]	Morse and Hammes, 1974[330]
	Friend et al., 1997[203]	Motycka and Nairn, 1979[89]
	Gantt et al., 2000[37]	Nakajima et al., 1987[331]
	Golzi et al., 2004[95]	Powell, 1993[198]
	He and Hou, 1989[178]	Powell and Anderson, 1971[107]
	Inoe, 1992[204]	Safwat and El-Shanawany, 1989[71]
	John, 1979[205]	Samejima et al., 1982[106]
	Kato, 1981[79]	Takashima et al., 1985[332]
	Kato and Nemoto, 1978[277]	JP 01005004 B4; Anon., 1981[333]
	Kato and Nemoto, 1978[334]	Venkatesh and Kramer, 2003[38]
	Kato et al., 1979[278]	Wieland-Berghausen et al., 2002[192]

The references are arranged in similar format to those in Table 1. Table 17 is continued in the appendix.

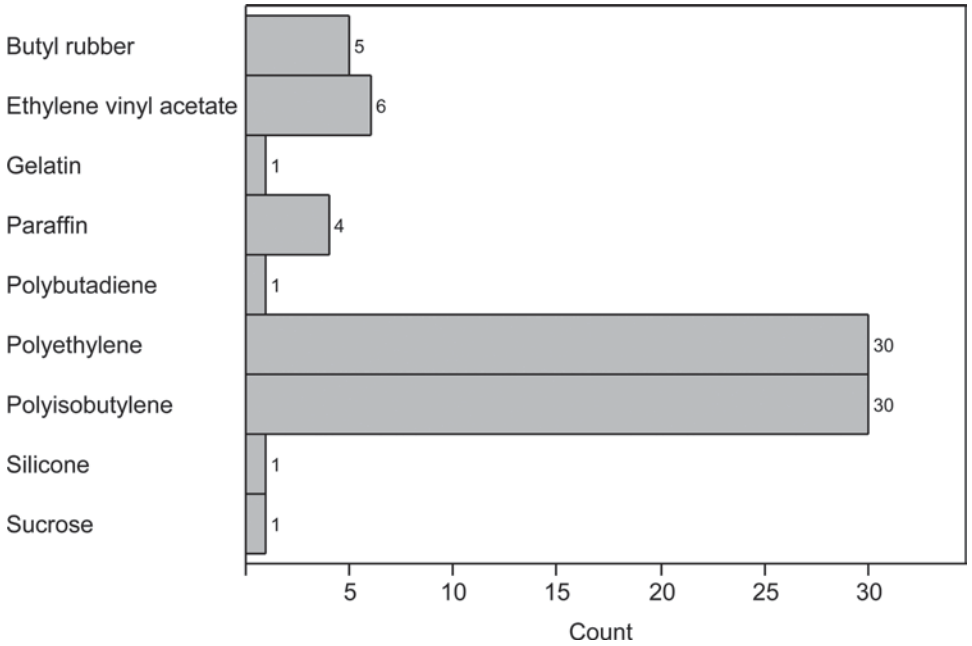

Figure 6. A list of protective colloids commonly used during microencapsulation along with the frequency by which each protective colloid was identified in the literature.

barrier uniformity. Koida et al. concluded that microcapsules exhibiting the greatest extents of modified release were produced when wall compactness, thickness and uniformity were balanced and optimized as functions of the PIB MW combination utilized.

Plasticizers

Five references were identified where the influence of plasticizer on microcapsule performance was investigated. In some of the studies, the influence of plasticizer was demonstrated via testing performance of

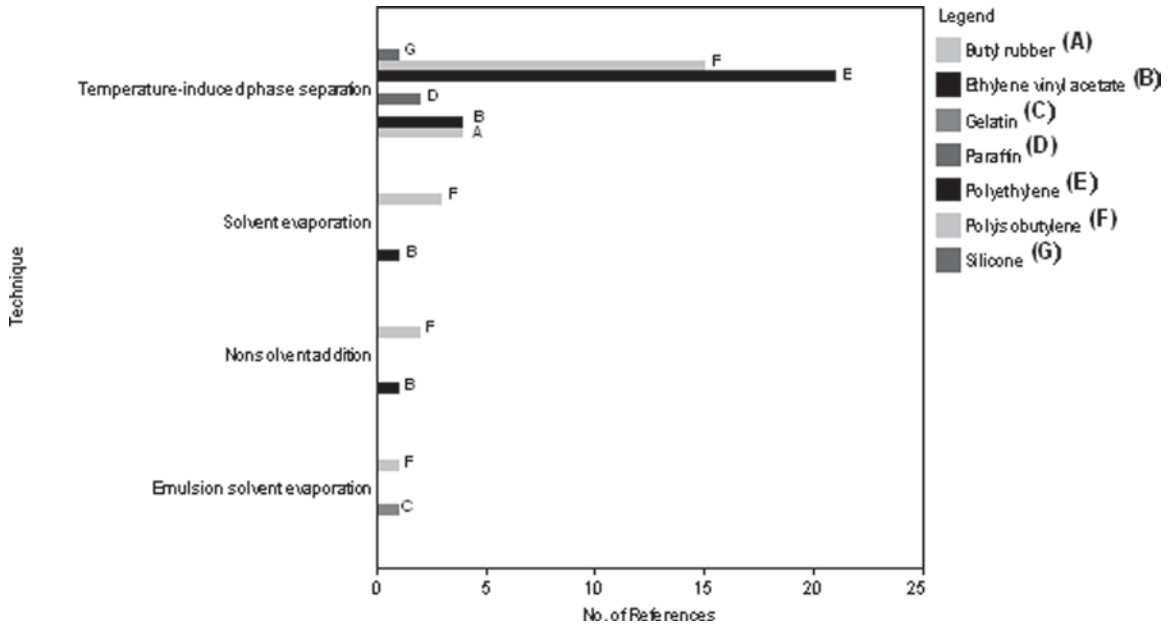

Figure 7. Referencing frequency of each protective colloid according to the microencapsulation technique used.

microcapsules formulated with or without plasticizer. In other studies, various plasticizers were evaluated in parallel to determine which plasticizer was most capable of achieving the desired endpoint, such as modified release. The presence of plasticizer often augmented modified release by increasing continuity of the microcapsule membrane and decreasing permeability.

Wan et al.[99] studied the influence of propylene glycol, glycerin and citric acid on the properties and performance of hypromellose microcapsules produced via spray drying. Improved flow property measurements, in general, indicated that addition of plasticizer increased cohesiveness of the spray-dried particles. Leaching of plasticizer from the barrier often resulted in the formation of pores, which increased API release rate. For example, dissolution of entrained triethyl citrate produced a porous honeycomb-like microcapsule wall, which allowed rapid API release. Citric acid, on the other hand, produced the slowest observed API release rate. The type of plasticizer also influenced API crystallinity. For instance, amorphous API was produced when citric acid or glycerin was included as plasticizer.

In another study, Al-Omran et al.[108] investigated the effects of diethyl phthalate (DEP) and PEG 600 both at 20 and 40 weight percent of an encapsulating ethylcellulose barrier. Microcapsules produced with 20% PEG 600 dissolved very rapidly, but microcapsules containing 40% PEG 600 in the barrier dissolved much more slowly. The authors speculated that slower release of diclofenac sodium, used as model API, resulted from an increased viscosity of phosphate dissolution media due to the higher concentration of dissolved PEG 600. A different trend was observed when comparing the dissolution profiles of microcapsules containing 20% DEP (slower release) vs. 40% DEP (faster release). Al-Omran et al. stated that API release was faster with 40% DEP because DEP exhibits enteric dissolution properties. Hence, DEP rapidly dissolved in the phosphate buffer, thus creating a highly porous ethylcellulose barrier through which dissolved API could be released. Ethylcellulose barriers containing 40% DEP became more porous than those containing 20% DEP, so faster API release was observed accordingly. In general, the palatability of microencapsulated diclofenac sodium was significantly improved over non-encapsulated diclofenac sodium. Furthermore, Al-Omran et al. found that microcapsules formulated with DEP were more palatable than microcapsules formulated with PEG 600.

Using dibutyl sebacate (DBS) as plasticizer, Lippold et al.[109] studied barrier permeability and release of guaifenesin from ethylcellulose microcapsules as functions of plasticizer concentration, thermal post-treatment and storage time of ethylcellulose dispersion in the presence of plasticizer (before microencapsulation). Microcapsules were produced in a fluidized bed by spray coating guaiphenesin with aqueous ethylcellulose dispersion (Aquacoat; FMC BioPolymer, Philadelphia, PA) containing varying concentrations of DBS. Lippold et al. studied DBS concentrations of 11.5, 19.4 and 23.1% in the barrier membrane. They investigated dispersion storage times (in the presence of plasticizer) of 0, 9 and 57 days. They also studied 1-hr thermal post-treatments at 40, 50 and 68°C. Lippold et al. found that DBS concentration in the barrier was the most influential factor upon barrier permeability. Thermal post-treatment was found necessary to coalesce ethylcellulose particles when a DBS concentration of 11.5% was used. In contrast, low permeability values were obtained without thermal post-treatment when ethylcellulose barriers contained DBS levels of 19.4 and 23.1%. At these higher DBS concentrations, application of the ethylcellulose barrier occurred above the minimum film formation

temperature, so thermal post-treatment was unnecessary. In fact, thermal post-treatment of barriers containing higher DBS concentrations actually increased barrier permeability. Lippold et al. speculated that thermal post-treatment at higher DBS concentrations allowed DBS to penetrate into ethylcellulose pseudolatex particles more completely. More complete DBS penetration caused the ethylcellulose chains to become more flexible and assume loosened, metastable conformations. These changes resulted in increased barrier permeability.

Motyka and Nairn[89] studied the effects of various plasticizers on barrier permeability from ethylcellulose std 20 and std 100 microcapsules containing ion-exchange resin in the benzoate form. Butyl stearate and castor oil were classified as lipophilic plasticizers, whereas PE and a PE-paraffin combination were classified as highly lipophilic plasticizers. Motyka and Nairn found that addition of any of these plasticizers, regardless of lipophilicity, prolonged release of benzoate to a greater extent compared to microcapsules formulated without plasticizer. For example, addition of castor oil produced ethylcellulose std 100 microcapsules exhibiting nearly a 50% decrease in diffusion coefficient of benzoate. Moreover, Motyka and Nairn found that highly lipophilic plasticizers produced ethylcellulose microcapsules exhibiting the greatest resistance to benzoate release. In fact, ethylcellulose std 100 microcapsules formulated with the PE-paraffin plasticizer combination produced the greatest extent of modified release.

Surfactants

Surfactants have been shown to affect microcapsule properties, such as particle size and barrier permeability. Because of their surface active properties, surfactants typically facilitate production of finer, more homogeneous mixtures between immiscible phases in emulsions or suspensions. Facilitated mixing of immiscible phases can ultimately result in reduced microcapsule size.

References have been identified where inclusion of surfactants during microencapsulation either increased or decreased API release. It is not surprising that surfactants could increase API release. Polar regions of its amphiphilic molecular structure often facilitate dissolution of the surfactant in water. Hence, aqueous media could gain easier access to the microcapsule core via dissolution of surfactant embedded throughout the microcapsule barrier. That is, dissolution of embedded surfactant could create a porous network through which dissolution media could more rapidly penetrate and subsequently dissolve API. Surprisingly, surfactants have also been shown to augment modified release performance. Examples of both cases will be briefly discussed.

Chowdary and Nageswara[110] prepared ethylcellulose microcapsules containing sulfamethoxazole with or without Span 60 or Span 80 and studied the influence of surfactant on the resulting microcapsule properties. Inclusion of these surfactants decreased microcapsule size, but did not affect API release.

Fekete et al.[111,112] dissolved sodium dioctylsulfosuccinate, an anionic surfactant, and ethylcellulose in cyclohexane en route to producing microcapsules. The presence of sodium dioctylsulfosuccinate made possible the production of microcapsules exhibiting both suitable tabletting and rapid dissolution properties.

Singh and Robinson[113] produced microcapsules containing captopril with different viscosity grades of ethylcellulose. Nonionic surfactants alone or in combination with other nonionic surfactants were dissolved in ethanol and added to the coacervation system to ensure complete dissolution of ethylcellulose. Surprisingly, microcapsules prepared using ethylcellulose std 45 along with 2% polysorbate 80 exhibited the greatest extent of prolonged release of all microcapsule formulations studied. These microcapsules released 70% API at 55 min compared to 70% in 7.75 min from ethylcellulose microcapsules produced without surfactant. The prolonged release effect resulting from addition of polysorbate 80 was surprising because the surfactant is soluble in water and would be expected to increase, rather than decrease, API dissolution.

Review summary

This three-part publication series represents a comprehensive review of 379 references identified where ethylcellulose, methylcellulose or hypromellose was used for microencapsulation. In Part 1, covered in the current paper, the roles of ethylcellulose, methylcellulose and hypromellose in microencapsulation are discussed. Most of the literature communicates the use of ethylcellulose as an encapsulating polymer. Part 1 also describes the use of other materials that have been formulated with the aforementioned encapsulating polymers. Such ingredients are protective colloids, plasticizers and surfactants.

The various techniques identified to make microcapsules are discussed in Part 2, which is covered in a separate paper. Part 3, covered in a third paper, discusses the various end-use applications for which microcapsules are used. In conclusion, the intent for this review is to give the reader a basic understanding of how and why ethylcellulose, methylcellulose and hypromellose are utilized in microencapsulation.

Acknowledgment

The authors gratefully acknowledge Roland Adden for providing helpful insight regarding cellulose ether chemistries.

Declaration of interest

The authors are employed by The Dow Chemical Company.

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Appendix: Continuations of Tables 1, 10 and 17

Table 1 (continued). References identified where ethylcellulose was used for microencapsulation.

Ethylcellulose references		
Dahlström and Eriksson, 1971[174]	Farid et al., 1994[176]	Hecquet et al., 1984[335]
Dailey and Dowler, 1995[281]	Farivar et al., 1993[336]	Heintz and Teipel, 2000[319]
Dailey and Dowler, 1996[305]	Fekete et al., 1989[112]	Heintz et al., 2001[337]
Das, 1991[217]	Fekete, 1992[111]	Hirata and Niki, 1975[326]
Das, 1993[328]	Fernandez-Urrusuno et al., 2000[291]	Hitchcock, 1980[338]
Deasy et al., 1980[34]	Forni et al., 1991[262]	Hosny et al., 1998[180]
Deshpande and Njikam, 1977[284]	Friend et al., 1997[203]	Hsiao and Chou, 1989[12]
Dévay and Rácz, 1984[339]	Fukumori et al., 1991[248]	Hu et al., 1999[272]
Dévay and Rácz, 1987[340]	Fukumori et al., 1991[249]	Huang and Ghebre-Sellassie, 1989[222]
Dobetti et al., 1999[327]	Gantt et al., 2000[37]	Ibrahim et al., 1990[238]
Donbrow and Benita, 1977[101]	Gentilini, 1986[341]	Ichikawa and Fukumori, 2000[72]
Doshi et al., 1994[199]	Georgiev et al., 1994[69]	Inoe, 1992[204]
Dragan et al., 1985[31]	Ghorab et al., 1990[237]	Ishibashi et al., 1984[92]
Du et al., 2001[263]	Giannini and Bashour, 1989[97]	Ishibashi et al., 1984[93]
Dubernet et al., 1990[342]	Gold, 2001[294]	Ishibashi et al., 1985[91]
Dubernet et al., 1991[236]	Golzi et al., 2004[95]	Itoh et al., 1980[259]
Ducroux et al., 1984[287]	Goto, 1994[295]	Jalsenjak et al., 1980[182]
Dyug et al., 1982[343]	Goto et al., 1973[297]	Jani et al., 1992[344]
Echigo et al., 1982[289]	Goto et al., 1976[345]	John, 1979[205]
El-Helw, 1987[201]	Goto et al., 1984[88]	Jones and Pearce, 1995[223]
El-Helw and Nixon, 1987[346]	Goto et al., 1985[32]	Jouffroy, 1984[308]
El-Helw et al., 1988[347]	Guo and Xu, 1998[298]	Kaeser-Liard et al., 1984[348]
El-Helw and Bayomi, 2000[257]	Guyot and Fawaz, 1998[41]	Kallstrand et al., 1986[321]
Elbahri and Taverdet, 2005[219]	Han and Li, 2001[250]	Kaltsatos et al., 1989[189]
Elbary et al., 2001[66]	Harte, 1978[318]	JP 58035111 A2; Anon., 1981[265]
Eley et al., 1992[306]	Hasan et al., 1992[349]	Kantor et al., 1989[322]
Fan et al., 1996[202]	He and Hou, 1989[178]	Karakasa et al., 1994[274]
Kassem et al., 1975[184]	Kristl et al., 1991[209]	Moldenhauer and Nairn, 1992[84]
Kassem et al., 1978[81]	Kristmundsdottir and Ingvarsdottir, 1994[242]	Moldenhauer and Nairn, 1994[83]
Kato, 1981[275]	Ku and Kang, 1991[243]	Morishita et al., 1973[231]
Kato and Nemoto, 1978[277]	Lavasanifar et al., 1997[285]	Morishita et al., 1976[233]
Kato and Nemoto, 1978[334]	Lee et al., 1984[33]	Morishita et al., 1981[212]
Kato et al., 1979[278]	Liao et al., 2003[267]	Morishita et al., 1985[165]
Kato, 1981[79]	Lin, 1985[210]	Morre et al., 2002[166]
Kato et al., 1985[310]	Lin et al., 1985[104]	Morris and Warburton, 1982[52]
Kawashima et al., 1984[102]	Lin and Yang, 1986[187]	Morse, 1971[59]
Kentepozidou and Kiparissides, 1995[225]	Lin et al., 1988[290]	Morse and Hammes, 1972[316]
Khalil and El-Gamal, 1973[239]	Lin and Chen, 1992[190]	Morse and Hammes, 1974[193]
Khanna et al., 1982[77]	Lin and Wu, 1999[229]	Morse and Hammes, 1974[330]
Kim et al., 1999[251]	Lin et al., 2004[264]	Morse et al., 1978[194]
Kimura, 1971[350]	Lippmann et al., 1981[11]	Mortada, 1982[213]
Kimura et al., 1999[280]	Lippold et al., 1989[109]	Motycka and Nairn, 1979[89]
Kiritani, 1973[227]	Mallick et al., 1999[351]	Motycka et al., 1985[87]
Kitajima et al., 1969[352]	Mallick et al., 2002[353]	Murai et al., 1971[354]
Kitakoji et al., 1973[266]	Manekar et al., 1992[245]	Murav'ev and Andreeva, 1987[167]
Knezevic et al., 1998[252]	Manekar et al., 1992[234]	Murgu et al., 1981[301]
Koida et al., 1983[40]	Manekar et al., 1993[235]	Murthy and Chowdary, 2004[96]
Koida et al., 1984[103]	Mao and Zhang, 1994[268]	Murthy and Chowdary, 2005[214]
Koida et al., 1986[208]	Maysinger and Jalsenjak, 1983[292]	Nakajima et al., 1987[331]
Kondo et al., 1972[186]	Meier et al., 1974[51]	Nasa and Yadav, 1989[195]
Kondo and Ueda, 1973[329]	NL 7215117 A; Anon., 1974[164]	NL 6611661; Anon., 1967[196]
Kosenko et al., 1986[241]	Miller and Anderson, 1964[6]	Nelson, 1974[355]
Kostova et al., 1994[68]	Moldenhauer and Nairn, 1990[86]	Nemoto and Kato, 1981[302]

Table 1. continued on next page

Table 1. Continued.

Ethylcellulose references		
Kozlova et al., 1977[282]	Moldenhauer and Nairn, 1991[85]	Nemoto and Kato, 1984[303]
Nikolaev et al., 1990[168]	Rhee et al., 1997[67]	Singh and Robinson, 1988[113]
Nikolayev and Gebre-Mariam, 1993[169]	Ruiz et al., 1990[218]	Singh and Robinson, 1990[30]
Nimmannit and Suwanpatra, 1996[356]	Safwat and El-Shanawany, 1989[71]	Singla and Nagrath, 1988[53]
Nixon and Agyilirah, 1982[105]	Sajeev et al., 2002[172]	Snipes and Wagner, 1989[74]
Nixon and Meleka, 1984[255]	Sakr, 1991[357]	Sriwongjanya and Bodmeier, 1997[82]
Nixon and Nimmannit, 1985[256]	Sakuma and Atsumi, 1990[317]	Suryakusuma and Jun, 1984[358]
Nixon and Wong, 1990[197]	Salib, 1973[359]	Suryakusuma and Jun, 1984[360]
Oh and Lee, 1982[361]	Salib et al., 1976[258]	Sveinsson and Kristmundsdottir, 1992[206]
Okamoto et al., 1986[296]	Salib et al., 1989[362]	Szretter and Zakrzewski, 1984[207]
Öner et al., 1983[363]	Samejima, 1985[15]	Szretter and Zakrzewski, 1984[364]
Öner et al., 1984[365]	Samejima et al., 1982[106]	Szretter and Zakrzewski, 1987[366]
Öner et al., 1988[367]	Samejima et al., 1985[47,48]	Szretter and Zakrzewski, 1987[320]
Özyazici et al., 1996[170]	Samejima et al., 1985[47,48]	Takada, 2000[307]
Palomo et al., 1996[304]	Samejima et al., 1983[80]	Takashima et al., 1985[332]
Pandell and Temin, 1972[368]	Sarin et al., 1985[49]	Masayoshi and Goichi, 1981[369]
Perez-Martinez et al., 2001[215]	Senjkovic and Jalsenjak, 1984[254]	JP 01005004 B4; Anon., 1981[333]
Persson and Lindblom, 1981[253]	Sevgi et al., 1994[173]	JP 63007091 B4; Anon., 1982[370]
Portnyagina et al., 1991[299]	Sevgi et al., 1994[371]	Tanaka, 1978[279]
Powell and Anderson, 1971[107]	Sfar and Karoui, 1989[73]	Tateno et al., 1978[372]
Powell, 1993[198]	Shear and Kershman, 2000[373]	Tirkkonen and Paronen, 1993[177]
Putcha et al., 2005[300]	Shekerdzhiiski et al., 1988[374]	Titeva et al., 1986[375]
Raghubanshi et al., 1991[171]	Shekhare and Gupta, 1989[376]	Tomova et al., 1988[377]
Rak et al., 1984[200]	Sheorey et al., 1991[220]	JP 56049315 A2; Anon., 1980[378]
Rak et al., 1984[271]	Shin and Koh, 1989[75]	Tsai and Huang, 1985[55]
Rani et al., 1994[273]	Shindo, 1988[276]	Tsujiyama et al., 1989[46]
Rao et al., 2005[379]	Shopova and Tomova, 1982[380]	Tsujiyama et al., 1990[45]
Ravichandran et al., 2001[216]	Shopova et al., 1987[175]	Tuncel et al., 1996[179]
Uchida et al., 1987[240]	Yalabik-Kas, 1983[381]	
Uchida and Goto, 1988[283]	Yalabik-Kas, 1983[293]	
Uchida et al., 1989[286]	Yamada et al., 1996[270]	
Uchida et al., 1992[44]	Yang et al., 2000[224]	
Uddin et al., 2001[39]	Yang et al., 2001[226]	
Unno et al., 1981[382]	Yang et al., 2001[228]	
Uno et al., 1984[221]	Yang et al., 2005[230]	
Utsuki et al., 1996[288]	Yazan et al., 1995[183]	
Venkatesh and Kramer, 2003[38]	Yazici et al., 1996[261]	
Vishwanath and Sharma, 1978[383]	Yokota et al., 1994[90]	
Vitek, 1978[384]	Yokoyama and Shibata, 1987[323]	
Vitkova et al., 1983[56]	Yoon and Yong, 1987[385]	
Vitkova et al., 1984[211]	Yoshida, 1972[244]	
Vitkova et al., 1986[181]	Yoshida et al., 1980[386]	
Vitkova et al., 1994[188]	Zandi et al., 1998[232]	
Vo et al., 2000[269]	Zhang et al., 1993[315]	
Wang et al., 1993[309]	Zhang et al., 2000[26,27]	
Wang et al., 1993[311]	Zhang et al., 2000[26,27]	
Wang et al., 1995[312]	Zhang, 2002[387]	
Wang et al., 1996[313]	Zhang et al., 2004[388]	
Weiss et al., 1998[389]	Zhelyazkova and Petrova, 1984[390]	
Whitaker Sr., 1991[191]	Zhelyazkova et al., 1985[391]	
Wieland-Berghausen et al., 2002[192]	Zhu et al., 1992[246]	
Williams et al., 1982[392]	Zia et al., 1991[185]	
Witz, 1982[393]	Zou et al., 1991[394]	
Wu et al., 1993[260]	Zulkarnain, 1996[247]	
Wu et al., 1994[43]		

Table 10 (continued). Application-oriented publications where microcapsules were utilized to achieve modified release.

Methylcellulose references	Hypromellose references
Cohen, 1986[152]	Ayer et al., 1994[98]
	Gold, 2001[294]
	Hasçiçek et al., 2003[100]

Table 17 (continued). References identified where protective colloids were utilized to make microcapsules.

Protective colloid	References	
Polyisobutylene	Barik et al., 1993[155]	Koida et al., 1984[103]
	Barik et al., 2004[60]	Kristl et al., 1991[209]
	Cameroni et al., 1985[141]	Lin, 1985[210]
	Carpov et al., 1982[144]	Moldenhauer and Nairn, 1990[86]
	Carpov et al., 1980[147]	Moldenhauer and Nairn, 1991[85]
	Chemtob, 1987[14]	Moldenhauer and Nairn, 1992[84]
	Chemtob et al., 1986[160]	Moldenhauer and Nairn, 1994[83]
	Chemtob et al., 1986[162]	Nixon and Agyilirah, 1982[105]
	Chemtob et al., 1989[115]	Samejima et al., 1985[47,48]
	Das, 1991[217]	Samejima et al., 1982[106]
	Das, 1993[328]	Shin and Koh, 1989[75]
	Donbrow and Benita, 1977[101]	Sveinsson and Kristmundsdottir, 1992[206]
	Hirata and Niki, 1975[326]	Tirkkonen and Paronen, 1993[177]
	Kawashima et al., 1984[102]	Uddin et al., 2001[39]
	Koida et al., 1983[40]	Wieland-Berghausen et al., 2002[192]
Silicone	Masayoshi and Goichi, 1981[369]	
Sucrose	Chikamatsu et al., 1984[76]	