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REVIEW ARTICLE

Reviewing the use of ethylcellulose, methylcellulose and hypromellose in microencapsulation. Part 3: Applications for microcapsules

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Abstract

This three-part review has been developed following the evaluation of literature where ethylcellulose, methylcellulose, or hypromellose was used to make microcapsules. Parts 1 and 2 of the review are published in separate papers. Part 1 covers the various materials used to formulate microcapsules, and Part 2 covers the various techniques used to make microcapsules. In the current paper, Part 3 covers the end-use applications for which microcapsules are used. Examples of applications to be covered include modified release, improved efficacy and safety, multiparticulate compression, improved processability and stability, and taste- and odor-masking. It is hoped that formulators can use Part 3 to understand the various end-use applications of microcapsules made from these encapsulating polymers. SciFinder was utilized to perform the literature search. 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

This review has been developed following the evaluation of literature where ethylcellulose, methylcellulose, or hypromellose was used to make microcapsules. The review has been divided into three sections. The first section is focused upon materials used to formulate microcapsules, such as the three encapsulating polymers: ethylcellulose, methylcellulose, and hypromellose, as well as protective colloids, plasticizers, and surfactants. The second section is focused upon various techniques used to make microcapsules, such as temperature-induced phase separation, emulsion solvent evaporation, solvent evaporation, film coating, nonsolvent addition, and spray drying. The objective of the third section, covered in the current paper, is to discuss various applications for which microcapsules are used, such as modified release, improved efficacy and safety, multiparticulate compression, improved processability and stability, and taste- or odor-masking.

A total of 379 references were identified during the literature review. Because of the extensive amount of literature, this review has been divided into three parts corresponding with the three sections described above. The search methodology utilized to obtain the references is covered in detail in Part 1. In addition, Part 1 may be referred to for a more in-depth introduction.

End-use applications

Of the 379 references, 133 were identified, which focused upon end-use applications for microcapsules. End-use applications are shown in Figure 1 by the frequency at which each was identified in the application-based

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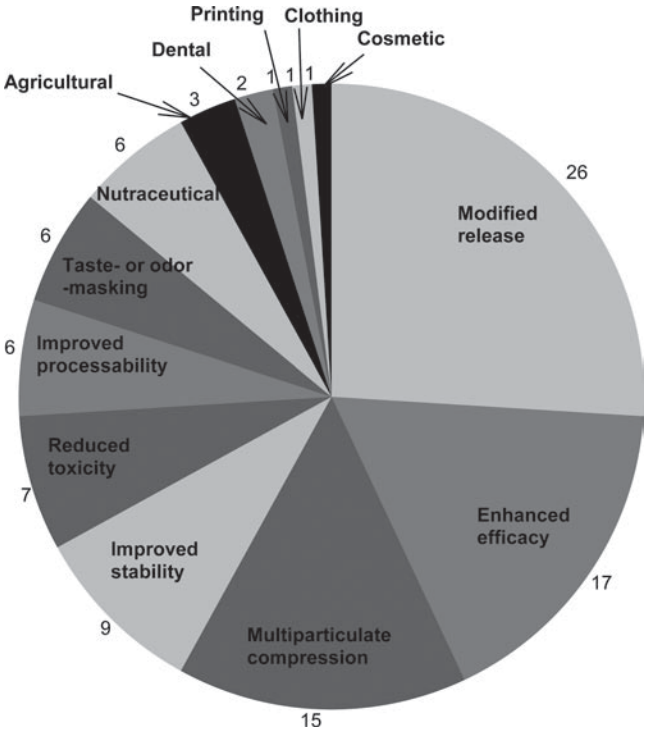

Figure 1. Pie chart analysis, by end-use application, of the 133 application-oriented references identified in this literature review. Each number on the pie chart represents the percentage of the application-oriented references where the respective application space was targeted.

literature. These applications will be discussed throughout the remainder of the paper.

Modified release

A modified release dosage form is defined in the Encyclopedia Britannica as one developed to deliver drug to part of the body where it will be absorbed, to simplify dosage regimens, and to assure that therapeutic drug levels are maintained over appropriate time intervals (see ref. 1). Modified release is the most common of all end-use applications identified for microcapsules. As illustrated in Figure 1, 26% of the 133 application-based references communicate the use of microcapsules to achieve modified release. These references are listed in Table 1. Being that ethylcellulose is a water-insoluble polymer, the primary objective of many of the studies was to achieve modified release through an insoluble ethylcellulose barrier. Studies were reviewed where ethylcellulose microcapsules modified active pharmaceutical ingredient (API) release over a time period ranging from a few hours (h)[2–6] to as long as several days[7,8].

Extended release is a type of modified release readily achievable with ethylcellulose. The USP33-NF28 defines an extended release dosage form as one that is formulated in such manner to make the contained medicament available over an extended period of time following ingestion[9]. A more detailed description of extended release is provided by Collett and Moreton[10]. Collett and Moreton state that extended release dosage forms release API slowly, so that plasma concentrations are maintained

Table 1. Application-oriented publications where microcapsules were utilized to achieve modified release. References are listed alphabetically by the first author's or inventor's last name. Table 1 is continued in the appendix.

Ethylcellulose references		
Adikwu, 1995[197]	Hsiao and Chou, 1989[198]	Raghubanshi et al., 1991[142]
Alpar, 1981[137]	Hu et al., 1999[118]	Rak et al., 1984[100]
Alpar and Walters, 1981[163]	Ishibashi et al., 1985[199]	Rani et al., 1994[155]
Ayer et al., 1994[109]	Jalsenjak et al., 1980[6]	Sajeev et al., 2002[39]
Baichwal and Abraham, 1980[12]	Karakasa et al., 1994[112]	Samejima et al., 1985[200]
Bergisadi and Gurvardar, 1989[2]	Kato, 1981[119]	Sevgi et al., 1994[88]
Biju et al., 2004[115]	Kato and Nemoto, 1978[102]	Shindo, 1988[104]
Chukwu et al., 1991[165]	Kato et al., 1979[129]	Shopova et al., 1987[114]
Cohen, 1986[97]	Kimura et al., 1999[120]	Tanaka, 1978[177]
Curea et al., 1987[110]	Kondo et al., 1972[140]	Tsai and Huang, 1985[13]
Dailey and Dowler, 1995[178]	Kozlova et al., 1977[175]	Tsujiyama et al., 1990[117]
Deshpande and Njikam, 1977[5]	Lavasanifar et al., 1997[61]	Uchida and Goto, 1988[201]
Ducroux et al., 1984[98]	Lee et al., 1984[23]	Uchida et al., 1989[50]
Echigo et al., 1982[128]	Lin et al., 1988[7]	Utsuki et al., 1996[8]
Fernandez-Urrusuno et al., 2000[180]	Lippmann et al., 1981[134]	Venkatesh and Kramer, 2003[144]
Gantt et al., 2000[138]	Maysinger and Jalsenjak, 1983[202]	Vitkova et al., 1986[135]
Georgiev et al., 1994[93]	Morales et al., 2010[203]	Yalabik-Kas, 1983[204]
Gold, 2001[99]	Morre et al., 2002[141]	Yazan et al., 1995[145]
Golzi et al., 2004[166]	Murav'ev and Andreeva, 1987[34]	Yokota et al., 1994[167]
Goto, 1994[205]	Nikolayev and Gebre-Mariam, 1993[113]	Zia et al., 1991[146]
Goto et al., 1973[95]	Okamoto et al., 1986[103]	
Guo and Xu, 1998[111]	Özyazici et al., 1996[148]	
He and Hou, 1989[174]	Portnyagina et al., 1991[116]	
Hosny et al., 1998[139]	Putcha et al., 2005[106]	

at a therapeutic level for a prolonged time period (usually between 8 and 12 h).

Weiss et al. produced ethylcellulose microcapsules containing a rennin-inhibitor tripeptide for once-daily administration[11]. The nonencapsulated API exhibited pH-dependent solubility due to its existence as a hydrochloride salt. Once microencapsulated, however, the API was released in extended fashion almost identically when the microcapsules were introduced into aqueous dissolution media at either pH 1.2 or pH 6.0. The ethylcellulose barrier made possible the formation of an acidic microenvironment inside each microcapsule. Dissolution media gradually diffused across the ethylcellulose barrier into the microcapsule core and dissolved the API salt, thus rendering an acidic microenvironment. Similar extended release profiles occurred regardless of dissolution media pH due to a consistently acidic microenvironment inside each microcapsule.

It should be noted that dissolution media first penetrates the barrier membrane in order to gain access to the microcapsule core and dissolve the API. The dissolved API must then traverse back across the barrier membrane to be released outside of the microcapsule[10]. Both dissolution media penetration into, and diffusion of dissolved API out of, the microcapsule typically occur in extended fashion across the ethylcellulose barrier. Extended API release across the barrier can be modulated using pore-forming additives, varying the viscosity grade of ethylcellulose, or varying the amount of ethylcellulose barrier applied.

Pore-forming additives, or pore-formers, are usually water-soluble or dispersible and are distributed throughout the ethylcellulose barrier. Pore-formers typically dissolve when microcapsules are introduced into aqueous dissolution media. Each newly formed void, previously occupied by pore-former, serves as a channel through which dissolution media can penetrate into, and dissolved API can be released from, the microcapsule. Baichwal and Abraham formulated ethylcellulose microcapsules containing metronidazole with varying levels of polyethylene glycol (PEG) 4000 in the barrier[12]. Overall, microencapsulated metronidazole was released more slowly than nonencapsulated metronidazole, but microencapsulated API release rates increased as the level of PEG 4000 increased. Faster release rates were likely due to formation of pores in the barrier as PEG 4000 dissolved. Higher levels of PEG 4000 led to the formation of a greater number of pores and/or larger pore sizes in the barrier. In a second example, Tsai and Huang formulated ethylcellulose microcapsules with or without PEG 4000 in order to modulate the release rate of indomethacin[13]. Like Baichwal and Abraham, Tsai and Huang found that microencapsulation within ethylcellulose modified indomethacin release, but ethylcellulose microcapsules containing PEG 4000 released indomethacin more rapidly than those formulated without PEG 4000. Furthermore, i*n vivo* studies revealed that ethylcellulose microcapsules with or without PEG 4000 prolonged blood levels of indomethacin, but those containing PEG 4000 produced higher plasma concentrations. In yet another example, Jani et al. used PEG 4000 as a "channeling" agent, and the barrier concentration of PEG 4000 could be varied in order to achieve the desired indomethacin release profile from ethylcellulose microcapsules[14].

Studies have revealed that the viscosity grade of ethylcellulose has significant impact on API release from microcapsules. Assimopoulou and Papageorgiou studied alkannin release as a function of various microencapsulation parameters, including ethylcellulose viscosity grade[15]. Alkannin release was modified to a greater extent from microcapsules formulated with ethylcellulose Std 45 versus those formulated with ethylcellulose Std 10. Other research groups have published similar findings[16–20].

The viscosity grade of ethylcellulose is directly proportional to its molecular weight (MW). A film-forming polymer of higher MW typically produces a more durable and continuous barrier compared to the same polymeric chemistry of lower MW, provided the viscosity and surface tension of the polymer-containing solution are sufficiently low to allow uniform polymer deposition and coalescence across a substrate surface. Consequently, a barrier composed of a higher MW polymer typically modifies API release to a greater extent compared to a barrier composed of the same polymeric chemistry, but of lower MW. Hence, the majority of related studies report that a greater degree of extended release can be achieved when a higher viscosity grade of ethylcellulose is used for microencapsulation.

For instance, Singh and Robinson investigated the effect of ethylcellulose viscosity grade and polymeric solution viscosity on barrier membrane formation[21]. Ethylcellulose viscosity grades of 10, 50, 100, and 300 cP and barrier:core ratios of 1:1, 2:1, and 3:1 were investigated. Since the concentration of captopril suspended in the microencapsulation system (200 mL cyclohexane containing 2% absolute alcohol) was kept constant, higher barrier:core ratios produced higher polymeric solution viscosities. Ethylcellulose of 300 cP viscosity grade was found unsuitable for microencapsulation due to incomplete barrier formation at all barrier:core ratios investigated. Viscosities of solutions containing the 300-cP viscosity grade were all too high for uniform coverage of the substrate surfaces. At a barrier:core ratio of 1:1, microcapsules produced using the 50 cP viscosity grade modified API release more so than those produced using the 10 cP viscosity grade, and microcapsules produced using the 100 cP viscosity grade exhibited the slowest API release. At a barrier:core ratio of 2:1, microcapsules produced using the 50 cP viscosity grade exhibited the slowest API release. At a barrier:core ratio of 3:1, microcapsules produced using the 10 cP viscosity grade exhibited the slowest API release, i.e. lower ethylcellulose viscosity grades became more efficacious at modulating API release as polymeric solution viscosity increased.

In contrast, some groups have reported increased API release rates when higher viscosity grades of ethylcellulose were used to formulate microcapsules[22–25]. Lee et al.[23]

provided an explanation for this phenomenon, which is consistent with the findings of Singh and Robinson[21]. Lee et al. found that barrier porosity increased when higher viscosity grades of ethylcellulose were used for microencapsulation. Increased barrier porosity may have resulted from the inability of a solution containing a higher viscosity grade ethylcellulose to completely encapsulate the microcapsule core.

Finally, extended release can be modulated by varying the amount of ethylcellulose barrier applied. Throughout the literature evaluation, the amount of ethylcellulose barrier applied was referred to as drug–polymer ratio, coating–core ratio, core–wall ratio, and wall thickness. For consistency, the amount of ethylcellulose barrier applied is referred to, in this review, as the barrier:core ratio. Several studies reported that API release became increasingly modulated as a greater amount of barrier was applied[3,4,13,23,26–43]. For example, Salib found that phenobarbitone dissolution could be adjusted by varying the barrier:core ratio during microencapsulation[40]. First, ethylcellulose microcapsules were formulated where the barrier:core ratio was 35:65 and complete API release was observed within 80 min. When the barrier:core ratio was increased to 50:50, the time for complete API release increased to 120 min. When the barrier:core ratio was further increased to 68:32, the time for complete API release increased to 180 min.

To conclude, extended release is a type of modified release where API is released slowly so that plasma concentrations can be maintained at a therapeutic level for a prolonged time period. Extended release barrier membranes typically are formulated from ethylcellulose and are insoluble in aqueous media over the physiological pH range. Extended release can be modulated via adjusting a number of factors, such as barrier porosity, ethylcellulose viscosity grade, and barrier:core ratio.

Modified release applications are further discussed in the following sub-sections:

- Kinetic modeling;
- pH-dependent release;
- Customized release;
- Parenteral delivery;
- Nasal delivery;
- Suppositories; and
- Topical delivery.

Kinetic modeling

During the literature review, a large number of references were identified where API dissolution from ethylcellulose microcapsules was fitted to various mathematical models in order to characterize release kinetics. Some of the more frequently identified kinetic models will be elaborated upon.

Fifteen references were identified where API release was fitted to first-order kinetics[5,6,19,21,27,44–53]. The first-order release model is also known as the exponential model[27]. Readers wanting to learn more about first-order release kinetics should refer to the work of Baker and Lonsdale[54]. Briefly, first-order kinetics can be described using Fick's first law (Eq. (1)).

$$J = -D\frac{dC}{dx} \tag{1}$$

where J is flux and D is diffusion coefficient; dC/dx is the concentration gradient where C is concentration in g/cm^3 and x is distance (cm) of movement perpendicular to the barrier surface[55]. First-order kinetics occur when API is released from a solid dosage form where the API source does not exist in excess solid form. (For comparison, refer to the later subsection on zero-order release.) The API is dissolved and diffuses out of the dosage form, thus increasingly depleting the API source. The API release rate decreases exponentially as drug continues to be depleted from the dosage form.

Singh and Robinson produced microcapsules that released API according to first-order kinetics[49]. They prepared microcapsules containing captopril using various viscosity grades of ethylcellulose. Microcapsules prepared using ethylcellulose Std 45 with 2% polysorbate 80 exhibited the greatest extent of modified release. The modified release profile was fitted to several models, and the profile most closely fit first-order kinetics.

Thirteen references were identified where the Higuchi model, also known as the square-root-of-time model, was used to describe release kinetics from microcapsules[23,27,29,56–65]. The Higuchi model, like the first-order model, is derived from Fick's first law (Eq. (1)), and Martin described its derivation from Equation (1) to obtain Equation (2)[55].

$$Q = \left[D\left(2A - C_S\right)C_S t\right]^{\frac{1}{2}} \tag{2}$$

where Q is the amount of drug depleted per unit area matrix; D is the diffusion coefficient of API through the matrix; A is the total concentration of API in the matrix; C_S is the solubility of API in the matrix; t is time. Martin stated that C_S is significantly less than A, so Equation (2) is often simplified to Equation (3).

$$Q = \left(2ADC_S t\right)^{\frac{1}{2}} \tag{3}$$

Equations 2 and 3 were derived to characterize modified API release from a homogeneous polymer matrix-type dosage form[55], but an ethylcellulose microcapsule is not considered representative of what Martin referred to as a homogeneous polymer matrix-type dosage form (see Figure 2). Typically, a microcapsule consists of a core containing API enrobed within an insoluble ethylcellulose barrier, which may contain pore-formers. Despite this, Amperiadou and Georgarakis reported suitability of the Higuchi model for characterizing microencapsulated API release through a porous ethylcellulose barrier[27].

Higuchi modified Equation (2) to account for porosity and tortuosity in what Martin referred to as granular

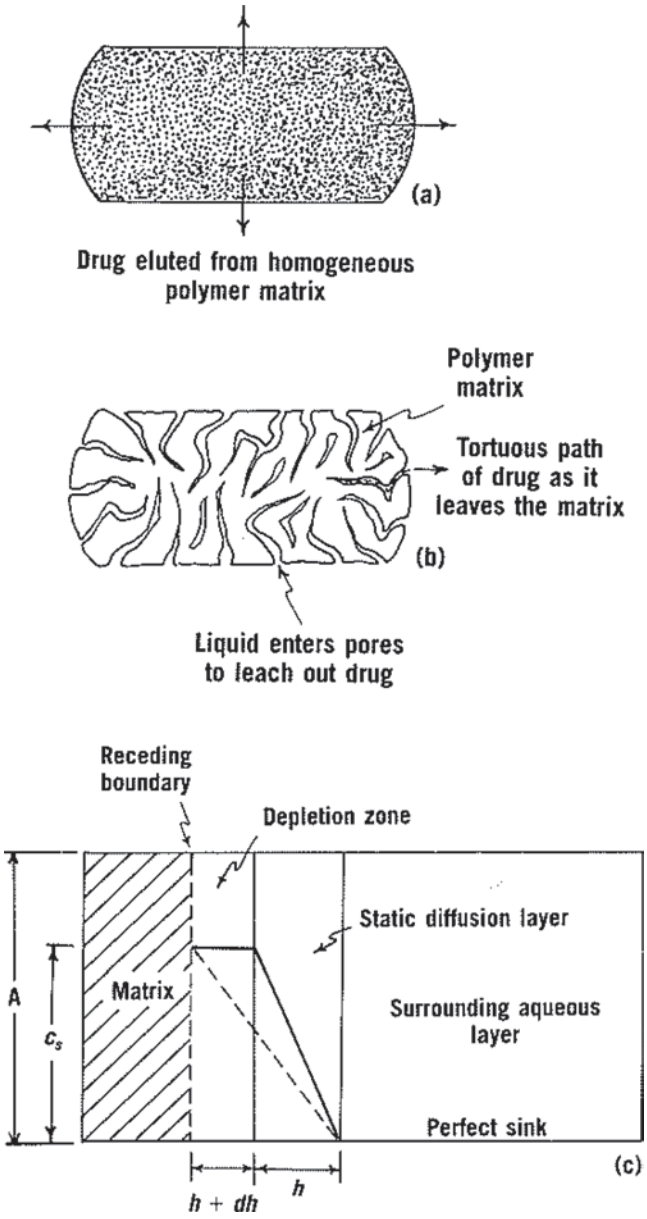

Figure 2. Figure from Martin et al. describing (A) homogeneous and (B) granular polymer matrices and (C) describing the kinetics of API release from these matrices according to the Higuchi model[55,196]. Reprinted with permission of Lippincott Williams & Wilkins[55]. Also reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.[196]

matrices (see Figure 2)[55]. The modified Higuchi equation is shown in Equation (4).

$$Q = \left[\frac{D_\epsilon}{\tau}\left(2A - \epsilon C_S\right)C_S t\right]^{\frac{1}{2}} \qquad \text{(Eq. 4)}$$

where ε is porosity of the granular matrix, and τ is tortuosity of the capillary system. Both ε and τ are dimensionless. It can be argued that the ethylcellulose barrier represents the granular matrix because it contains pores and tortuous channels through which dissolved API must diffuse in order to be released from the microcapsule. Hence, Equation (4) helps justify why several studies

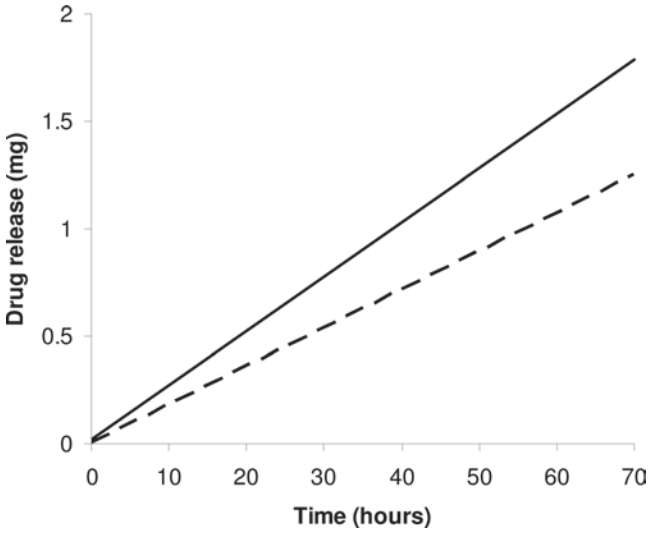

Figure 3. Example of two different steroids exhibiting zero-order release performance (steroid A: solid line; steroid B: dashed line).

have reported utility of the Higuchi model in characterizing API release kinetics from microcapsules.

Rama Rao et al. formulated ethylcellulose microcapsules in order to modify the release of zidovudine, and the Higuchi model provided the highest correlation when zidovudine release was fitted against several kinetic models[64]. In another study, Hasan et al. investigated modified release of diclofenac sodium from ethylcellulose microcapsules as a function of barrier:core ratio and fitted API release to the Higuchi, zero-order and first-order kinetic models[59]. Hasan et al. found that modified API release best fit the Higuchi model.

Six references were identified where modified API release fit zero-order kinetics[39,66–70]. For instance, Powell formulated ethylcellulose microcapsules containing calcium channel blockers like diltiazem, nifedipine, and verapamil[69]. The intent of the study was to formulate ethylcellulose microcapsules that released calcium channel blocker in zero-order fashion over 12 to 16 h. Zero-order kinetics occurs when API is released at a constant rate as illustrated in the two examples in Figure 3. As described by Martin, zero-order release is made possible when an excess source of undissolved API remains present in the dosage form[55]. The undissolved API serves as a depot from which API is dissolved and released at a constant rate. Like first-order kinetics, zero-order release can be described using Fick's first law (Eq. (1)).

Peppas et al. have published numerous studies on kinetic modeling[58,71–77]. Peppas et al. developed a simplified exponential model (Eq. (5)), which could be used to describe modified release kinetics of an API through a polymeric network regardless of dosage form shape or whether API diffusion was Fickian or non-Fickian[71,74,75].

$$\frac{M_t}{M_\infty} = kt^n \qquad (5)$$

where M_t is the mass of drug released at time, t; M_∞ is total mass of drug released as time approaches infinity; k is a constant that incorporates characteristics of the macromolecular polymeric network and API; n is the diffusional exponent indicating the drug release mechanism. Mallick et al. formulated ethylcellulose micropellets containing flurbiprofen at various drug loadings[78]. The API release data was fit to zero order, first order, Higuchi, Baker–Lonsdale, and Peppas equations, and also to the differential forms of the zero order, first order, and Higuchi models. Suitable correlations were found with the first order, Higuchi, and Peppas models, so these models were selected for F-test evaluation in order to determine which model most closely characterized API release. The F-test analysis revealed that the diffusional exponent model of Peppas most closely characterized flurbiprofen release.

Öner et al. used the Rosin–Rammler–Sperling–Bennet–Weibull (RRSBW) kinetic model to describe modified release of zinc sulfate from ethylcellulose microcapsules[79]. The RRSBW distribution, described by Langenbucher[80] in detail, is derived using the following equation.

$$\frac{m}{m_\infty} = 1 - \exp\left(-\frac{(t - t_0)}{\tau} \right)^\beta \qquad (6)$$

where m is the amount of API dissolved at time t; m_∞ is the amount of API dissolved after infinite time; t_0 is lag time; τ is the time at which 63.2% of the API is dissolved; and β is the shape parameter of the dissolution curve. Öner et al. converted Equation (6) to its logarithmic form shown in Equation (7).

$$\ln \ln \frac{1}{1 - \frac{m}{m_\infty}} = \beta \ln (t - t_0) - \beta \ln \tau \qquad (7)$$

Zinc sulfate release data fit suitably to Equation (7).

The API release from microcapsules often does not conform to one kinetic model[27,56,81–89]. For example, Amperiadou and Georgarakis[27], Nixon and Wong[86], and Yang et al.[89] formulated ethylcellulose microcapsules which released API according to combined first order and Higuchi kinetics. Chemtob et al. formulated ethylcellulose microcapsules that released metronidazole according to zero order and Higuchi kinetics[56]. Kristl et al. used various viscosity grades of ethylcellulose and protective colloid to formulate microcapsules containing bacampicillin[85], and API release fit combined zero- and first-order kinetics. Cameroni et al. reported that release kinetics changed as a function of the barrier:core ratio utilized[81]. Hixson–Crowell or Langenbucher kinetics were observed for microcapsules with wall thicknesses less than 5 μm, and Higuchi kinetics were observed for microcapsules with wall thicknesses greater than 5 μm.

pH-dependent release

Ethylcellulose is most often thought to form a pH-independent, rate-modulating barrier across the gastrointestinal (GI) pH range. Hence, a large number of studies was identified where ethylcellulose was used to formulate microcapsules for pH-independent extended release refer to the extended release discussion as well as the following referenced studies[11,90–92].

Six references were identified, however, where ethylcellulose microcapsules released API in pH-dependent fashion[22,24,67,93–95]. For example, Lippold and Förster found that release of undissociated API from ethylcellulose microcapsules occurred independently of pH if the microcapsules were formulated from organic solution-based systems[96]. Later, Lippold et al. formulated ethylcellulose microcapsules from plasticized Aquacoat ECD aqueous dispersion, and guaiphenesin release rate was found to be dependent upon pH[67]. Lippold et al. observed over a 2.5-fold increase in guaiphenesin release rate when ethylcellulose microcapsules were evaluated in dissolution media at pH 1.2 and 9.1, respectively. Lippold et al. speculated that the aqueous permeability of the microcapsule barrier was pH-dependent because of the occasional presence of carboxylic acid groups on the ethylcellulose molecules. Permeability of the ethylcellulose barrier increased as carboxylic acid moieties at ethylcellulose chain ends dissociated ($pK_a = 7.5$). Based upon these studies, it appears that pH-independent solubility is possible when ethylcellulose microcapsules are produced from organic systems, but pH-dependent solubility may occur when ethylcellulose microcapsules are produced from plasticized Aquacoat ECD dispersion.

Ghorab et al. found that 5-fluorouracil was released more rapidly from ethylcellulose microspheres when tested in acidic versus neutral media[94]. The 5-fluorouracil release was characterized in purified water and 0.1 N HCl, and release was more rapid in 0.1 N HCl. Ghorab et al. speculated that faster API release in 0.1 N HCl occurred due to the higher solubility of ethylcellulose in acidic media.

Customized release

A number of studies reported that microencapsulation parameters could be manipulated to produce dosage forms exhibiting customized API release[12,39,50,97–100]. As previously described, Baichwal and Abraham formulated microcapsules containing ethylcellulose and varying levels of PEG 4000 in the barrier membrane[12]. They found that progressively faster API release was achieved when higher levels of PEG 4000 were incorporated. Both Cohen and Sajeev et al. achieved specifically desired API release profiles by adjusting the thickness of the barrier membrane applied[39,97]. Thicker barrier membranes more effectively modified API release. Ducroux et al., Gold, and Rak et al. achieved specifically desired release profiles by formulating mixtures of encapsulated

and nonencapsulated API[98–100]. Nonencapsulated API provided immediate release properties, while encapsulated API provided modified release properties. When blended in certain proportions, the mixtures exhibited specifically desired API release profiles.

Parenteral delivery

Several groups have investigated the use of microcapsules for modified release via parenteral delivery [7,101–105]. Furthermore, a number of studies have demonstrated that parenteral delivery of microencapsulated API permits high target organ concentration along with reduced systemic levels. Kato and Nemoto microencapsulated mitomycin C within ethylcellulose for site-specific antineoplastic chemotherapy following intra-arterial infusion[102]. Kato and Nemoto claimed that microencapsulated mitomycin C made possible intense localized chemotherapy with less systemic toxicity compared to nonencapsulated mitomycin C. During *in vivo* studies, escape of microencapsulated mitomycin C from target tissue into the systemic circulation was only 40% relative to that observed with nonencapsulated mitomycin C. In a similar study, Eley et al. microencapsulated mitomycin C within ethylcellulose and investigated hepatic API concentration as well as cytotoxic effect on hepatic tumors following parenteral administration[101]. Microencapsulated mitomycin C was tested in a phase I clinical trial. Peak plasma levels from microencapsulated mitomycin C were significantly lower (80 versus 812 ng/mL), and localized hepatic concentrations were significantly higher than the corresponding levels achieved with nonencapsulated mitomycin C. In another study, Shindo found that ethylcellulose microcapsules containing peplomycin produced highly localized renal concentrations and localized cytotoxic effects following parenteral infusion compared to nonencapsulated peplomycin[104].

Lin et al. formulated microcapsules containing insulin using various types of encapsulating polymers with the intent of prolonging the hypoglycemic effect of insulin following parenteral administration[7]. Lin et al. investigated biodegradable encapsulating polymers, like polylactic acid and hypromellose phthalate (HP-55), and nonbiodegradable polymers, like ethylcellulose and ethylene vinylacetate (EVA). Ethylcellulose and ethylcellulose-EVA combinations produced microcapsules exhibiting the greatest duration of modified release, and suitable correlation was found between *in vitro* modified release and *in vivo* prolonged hypoglycemic effect. Parenteral administration of ethylcellulose microcapsules produced a hypoglycemic effect over 15 days, while administration of ethylcellulose-EVA microcapsules resulted in a hypoglycemic effect over 21 days.

Nasal delivery

Two references were found where hypromellose[60] and ethylcellulose[106] were used to encapsulate APIs for nasal delivery. Hasçiçek et al. formulated hypromellose microcapsules containing gentamicin sulfate, a highly polar antibiotic, to demonstrate that hypromellose could be used as a mucoadhesive polymer to increase contact time between API and nasal mucosa[60]. Hasçiçek et al. hypothesized that increasing contact time between API and nasal mucosa would increase systemic absorption. An *in vitro* test developed by Ranga Rao and Buri[107] was used to quantitate the mucoadhesive properties of microspheres upon exposure to excised sections of rabbit intestine. A higher barrier:core ratio (i.e. a higher amount of hypromellose) produced a higher degree of mucoadhesion. A higher barrier:core ratio also produced a slower release rate which fit Higuchi kinetics. Median particle size of the microspheres ranged from 13 to 25 μm. Such a size range was considered suitable for intranasal administration. Hasçiçek et al. concluded that *in vitro* performance properties of the microspheres were indicative of the potential for systemic intranasal absorption of gentamicin sulfate.

Putcha et al. microencapsulated APIs for mucosal administration, particularly via the intranasal route[106]. Microcapsules were designed to deliver phenothiazine derivatives for treatment of motion sickness. Putcha et al. claimed that API could be systemically absorbed from the microcapsules and avoid first-pass metabolism, or API could be delivered directly to the central nervous system via the axonal nerve found in the ostium (i.e. bypassing the blood-brain barrier). Microcapsules were designed using ethylcellulose Std 10 as encapsulating polymer in order to modify API release and consequently reduce the API's cytotoxic effect upon nasal mucosal cells. Putcha et al. claimed that the microencapsulated API release rate could be designed to equal its corresponding absorption rate. Hence, accumulation of API in the nasal mucosa could be avoided.

Suppositories

Nakajima et al. formulated suppositories containing indomethacin microencapsulated within ethylcellulose with the goal to release indomethacin in zero-order fashion[68]. Ethylcellulose microcapsules released indomethacin too slowly when polyethylene (PE) was used as a coacervation-inducing agent. Treating indomethacin with Hiviswako 104 (polyacrylic acid derivative) prior to microencapsulation produced a suppository formulation exhibiting zero-order kinetics at a desirably faster API release rate. Safwat and El-Shanawany also surface-treated theophylline and oxyphenbutazone with a polyacrylic acid derivative, microencapsulated within ethylcellulose, and finally formulated suppositories[108]. Pretreatment of the APIs with polyacrylic acid derivative prior to microencapsulation yielded suppositories exhibiting pseudo zero-order release kinetics.

Topical therapy

Cohen microencapsulated astringent for topical administration, particularly to the gums[97]. The astringent composition was made by producing ethylcellulose

Table 2. Application-oriented publications where microcapsules were utilized to enhance efficacy. No references were identified where methylcellulose microcapsules were used to enhance efficacy. The references are arranged in similar format to those in Table 1.

Ethylcellulose references		Hypromellose references
Ayer et al., 1994[109]	Murgu et al., 1981[125]	Ayer et al., 1994[109]
Barzola et al., 2001[132]	Nemoto and Kato, 1981[121]	Hasçiçek et al., 2003[60]
Beatty, 1982[123]	Nemoto and Kato, 1984[122]	
Biju et al., 2004[115]	Nikolayev and Gebre-Mariam, 1993[113]	
Curea et al., 1987[110]	Okamoto et al., 1986[103]	
Dahlstrom and Eriksson, 1971[133]	Palomo et al., 1996[158]	
Dailey and Dowler, 1995[178]	Portnyagina et al., 1991[116]	
Dailey and Dowler, 1996[179]	Rao et al., 2009[131]	
Echigo et al., 1982[128]	Rak et al., 1984[100]	
Eley et al., 1992[101]	Shindo, 1988[104]	
Guo and Xu, 1998[111]	Takada, 2000[195]	
Hu et al., 1999[118]	Tsai and Huang, 1985[13]	
Jouffroy, 1984[181]	Tsujiyama et al., 1990[117]	
Karakasa et al., 1994[112]	Tuncel et al., 1996[126]	
Kato, 1981[119]	Uchida et al., 1989[50]	
Kato and Nemoto, 1978[102]	Utsuki et al., 1996[8]	
Kato et al., 1979[129]	Wang et al., 1993[206,207]	
Kato et al., 1985[105]	Wang et al., 1995[208]	
Kimura et al., 1999[120]	Wang et al., 1996[159]	
Lin et al., 1988[7]	Zhang et al., 1993[127]	
Matsumoto and Ugajin, 1989[130]		
Morishita et al., 1985[124]		

microcapsules containing ferrous sulfate. The API release rate was modulated by varying the thickness of the ethylcellulose barrier. The microcapsules were entrapped in gauze or sponge pads for administration to the gums. Cohen stated that ethylcellulose was a preferred encapsulating polymer due to its inert and nonallergenic properties. Ghorab et al. developed ethylcellulose microspheres in order to modify 5-fluorouracil release following topical administration to skin tumors[94]. The API release was modulated by varying the viscosity grade of ethylcellulose.

Efficacy

As listed in Table 2 and illustrated in Figure 1, 17% of the 133 application-based references discuss enhanced efficacy via microencapsulation. Microencapsulation has been used to enhance API efficacy via prolonged pharmacological effect[7,13,109–114], enhanced pharmacological activity[115,116], reduced dosage or increased time interval between dosings[117], and targeted delivery[8,101,103,104,118–122].

It has been well documented that microencapsulated APIs produce prolonged pharmacological effects. Prolonged pharmacological effects are thought to be due to prolonged blood levels resulting from modified release. For example, Karakasa et al. formulated ethylcellulose microcapsules containing phenytoin sodium[112]. Microencapsulated and nonencapsulated phenytoin sodium were subjected to *in vitro* dissolution testing, and microencapsulated phenytoin sodium dissolved significantly more slowly. *In vivo* testing was conducted in both rabbits and humans. Oral administration of microencapsulated phenytoin sodium to rabbits produced prolonged plasma concentrations. Furthermore, Karakasa et al. observed prolonged urinary excretion of phenytoin metabolites following oral administration to humans.

Microencapsulated API has, in some instances, produced higher pharmacological activity compared to nonencapsulated API. Diclofenac sodium, a nonsteroidal anti-inflammatory drug (NSAID), was microencapsulated using a combination of cellulose acetate phthalate (CAP) and ethylcellulose in a 10:90 weight ratio[115]. The barrier:core ratio was optimized at 1.5:1 (w/w). The major objective was to produce a microcapsule formulation for enteric release. The optimized microcapsule formulation was subjected to *in vivo* testing in male Wistar rats in order to determine its systemic efficacy and ulcerogenic effect on the mucosal cells of the stomach. Microencapsulated diclofenac sodium produced higher (77.6% versus 70.5% anti-inflammatory activity) and more prolonged (8 h versus 2 h) anti-inflammatory response compared to the marketed formulation. Examination of excised stomach showed no histological signs of mucosal cell damage.

Tsujiyama et al. produced microcapsules using a combination of ethylcellulose and hydroxypropylcellulose[117]. An ethylcellulose–hydroxypropylcellulose combination of 3:5 (w/w) performed optimally. Ethylcellulose–hydroxypropylcellulose microcapsules containing piretanide were administered to spontaneously hypertensive rats in order to study both pharmacokinetic and

pharmacodynamic performance. The microcapsules were dosed at 10–30 mg API/kg body weight once daily, and a control solution of piretanide was dosed at 5–15 mg/kg twice daily. The microcapsules produced nearly identical area under the curve and antihypertensive response compared to the control solution. Tsujiyama et al. concluded that microcapsules produced suitable pharmacokinetic and pharmacodynamic performance even when administered at half the frequency of the oral solution.

Microcapsules have been used to target API delivery to specific sites within the body, a characteristic which could be exploited to both enhance efficacy and reduce systemic toxicity. Okamoto et al. reported targeted and prolonged antineoplastic activity with cisplatin microencapsulated within ethylcellulose[103]. Microcapsules were injected into the maxillary arteries of human patients suffering from tumors of the maxillary sinus or oral cavity. Following administration, systemic API levels from microcapsules were less than those observed with nonencapsulated cisplatin. A significantly higher API concentration, however, was found localized within the tumors. Okamoto et al. speculated that ethylcellulose microcapsules caused selective arterial infusion and micro-infarction once inside the tumors. Localization inside the tumors followed by prolonged release of microencapsulated cisplatin resulted in more intensive and prolonged antineoplastic effect within the tumors along with lower incidence of systemic toxicity.

Improved bioavailability

Some researchers have reported improved bioavailability from microencapsulated API[123–127]. Tuncel et al. formulated ethylcellulose microcapsules containing cephradine at a 1:1 barrier:core ratio[126]. The microcapsules were then mixed with microcrystalline cellulose and magnesium stearate and compressed to tablets. Both microcapsules and tabletted microcapsules containing 150 mg of cephradine were compared to a commercial capsule formulation containing 250 mg of cephradine. Even at a lower API dosage, both microcapsules and tabletted microcapsules produced higher bioavailabilities compared to the commercial capsule formulation.

Site-specific delivery

Several research groups have published studies where microcapsules were produced exhibiting magnetic properties for guided or site-specific delivery. External magnets could be used, for example, to guide magnetized microcapsules to the desired site of action[105,128–130]. Kato et al.[129] produced ethylcellulose microcapsules containing mitomycin C, and the microcapsules were added to a hexane dispersion containing zinc ferrite. The mixture was heated to 45°C and then cooled, thereby binding zinc ferrite to the microcapsule surface. *In vitro* testing confirmed that the microcapsules released mitomycin C in modified fashion. *In vivo* testing was conducted in dogs and rabbits. Microcapsules were successfully delivered to the aortas and renal arteries of dogs using an external magnetic field. Microcapsules were also successfully guided to treat bladder tumors in rabbits.

Rao et al. optimized a microsphere formulation containing ethylcellulose and hypromellose and designed to modulate release of rosiglitazone maleate specifically into the contents of the stomach[131]. It was found, through a 32-full factorial design, that ethylcellulose Std 7 concentration and stirring speed during microencapsulation most significantly impacted encapsulation efficiency, particle size, and API-release performance. Optimized microcapsules were approximately 350 μm in diameter, remained buoyant for over 12 h, and prolonged rosiglitazone release for 8 h.

Reproducibility

Several references were reviewed where microencapsulated API was used to achieve reproducible *in vitro* or *in vivo* performance[12,13,39,61,67,132]. Lavasanifar et al. formulated ethylcellulose microcapsules containing theophylline[61]. Five consecutive microcapsule batches were produced, and each batch exhibited suitable reproducibility regarding particle size and modified release performance.

Safety

As listed in Table 3 and illustrated in Figure 1, 7% of the application-based references discuss reduction of API toxicity via microencapsulation. For instance, microcapsules have shown significant potential to reduce GI irritability from APIs known to cause nausea, vomiting, diarrhea, or ulcers[23,61,115,125,132–135]. Recall from Part 1 that the Micro-K patent describes the detrimental effects of potassium chloride (KCl) upon GI mucosal cells and that microcapsules can be utilized to reduce the API's ulcerogenic

Table 3. Application-oriented publications where microcapsules were utilized to reduce toxicity. No references were identified where hypromellose microcapsules were used to reduce toxicity. The references are arranged in similar format to those in Table 1.

Ethylcellulose references	Methylcellulose references
Barzola et al., 2001[132]	Cohen, 1986[97]
Bergisadi and Gurvardar, 1989[2]	
Biju et al., 2004[115]	
Cohen, 1986[97]	
Dahlstrom and Eriksson, 1971[133]	
Dailey and Dowler, 1995[178]	
Eley et al., 1992[101]	
Fernandez-Urrusuno et al., 2000[180]	
Hsiao and Chou, 1989[198]	
Kato and Nemoto, 1978[102]	
Lavasanifar et al., 1997[61]	
Lee et al., 1984[23]	
Lippmann et al., 1981[134]	
Murgu et al., 1981[125]	
Nemoto and Kato, 1984[122]	
Okamoto et al., 1986[103]	
Putcha et al., 2005[106]	
Shindo, 1988[104]	
Vitkova et al., 1986[135]	

effect[134]. The KCl crystals were microencapsulated within ethylcellulose, and the microcapsules were subsequently blended with sodium lauryl sulfate (SLS). The mixture was then filled into hard-shell capsules. Following oral administration and subsequent capsule dissolution, SLS served to rapidly disperse the microcapsules. The act of rapidly dispersing the microcapsules prevented localization of KCl within one particular area of the GI tract. Ethylcellulose served as a barrier to modify the release rate of KCl. The microcapsule formulation was tested to determine its ulcerogenic effect upon feline duodenum, and the inventive formulation was compared against a wax-coated tablet formulation containing nonencapsulated KCl. Duodenum exposed to the microcapsule formulation was not damaged, but duodenum exposed to the wax-coated tablet formulation sustained extensive tissue damage in the area where the tablet settled.

The use of microcapsules for tumor-specific chemotherapy with minimal systemic toxicity was discussed earlier (see modified release and efficacy sections). Some speculate that retention of microcapsules inside tumors results from micro-infarction or chemoembolization upon perfusion into tumors[103,122]. Regardless of the mechanism, several groups have demonstrated that efficacy can be maximized and systemic toxicity minimized via targeted tumor delivery of microencapsulated antineoplastic APIs[102,103,122].

Multiparticulate compression

As illustrated in Figure 1, 15% of the 133 application-based references discuss compression of microcapsules. These references are listed in Table 4. Several research groups have formulated tablets containing microencapsulated API[6,12,13,34,39,88,109,113,114,133,136–146]. Most studies have been focused upon the condition and performance of the encapsulating barrier once compressed. References were identified where the barrier was not affected by compression as indicated by either no change in API release rate[12,13,113] or by the presence of distinctively intact microcapsules following compression[6,133,138,144]. References were found, however, where compression caused the barrier to rupture, thus allowing faster API release compared to that observed from the microcapsules before compression[143,145]. References were also identified where compression of microcapsules produced a fused, ethylcellulose matrix consisting of what were formerly individual microcapsule barriers. In these cases, the fused matrix modified API release to a greater extent than that observed from the microcapsules before compression[142,147].

Microcapsules have been utilized to improve physical properties of tablets. For example, Baichwal and Abraham formulated ethylcellulose microcapsules containing PEG and metronidazole[12]. The microcapsules were compressed, and resulting tablets were harder and less friable than tablets containing nonencapsulated metronidazole.

Dahlstrom and Eriksson found that tablets containing ferrous sulfate microencapsulated within ethylcellulose disintegrated more rapidly than tablets containing nonencapsulated ferrous sulfate[133]. Rapid tablet disintegration resulted in dissipation of microcapsules and lower incidence of GI irritation from ferrous sulfate. GI irritation was also minimized via prevention, by the barrier, of direct contact between ferrous sulfate and GI mucosal cells.

As mentioned above, several studies have demonstrated that microcapsules could be compressed to form tablets whereby the newly formed tablets contained distinctive, intact microcapsules. Jalsenjak et al., for example,

Table 4. Application-oriented publications where microcapsules were utilized for multiparticulate compression. No methylcellulose references were identified for this application. The references are arranged in similar format to those in Table 1.

Ethylcellulose references		Hypromellose references
Adikwu, 1995[197]	Anonymous, 1974[172]	Ayer et al., 1994[109]
Al-Omran et al., 2002[136]	Morishita et al., 1985[124]	
Alpar, 1981[137]	Morre et al., 2002[141]	
Alpar and Walters, 1981[163]	Murav'ev and Andreeva, 1987[34]	
Ayer et al., 1994[109]	Nikolaev et al., 1990[209]	
Baichwal and Chidambharam, 1977[168]	Nikolayev and Gebre-Mariam, 1993[113]	
Baichwal and Abraham, 1980[12]	Özyazici et al., 1996[148]	
Chikamatsu et al., 1984[164]	Raghubanshi et al., 1991[142]	
Chukwu et al., 1991[165]	Sajeev et al., 2002[39]	
Curea et al., 1987[110]	Sevgi et al., 1994[88]	
Dahlstrom and Eriksson, 1971[133]	Shopova et al., 1987[114]	
Farid et al., 1994[210]	Singla and Nagrath, 1988[161]	
Fekete, 1992[211]	Tirkkonen and Paronen, 1993[143]	
Gantt et al., 2000[138]	Tsai and Huang, 1985[13]	
He and Hou, 1989[174]	Tuncel et al., 1996[126]	
Hosny et al., 1998[139]	Venkatesh and Kramer, 2003[144]	
Hsiao and Chou, 1989[198]	Vitkova et al., 1986[135]	
Jalsenjak et al., 1980[6]	Yazan et al., 1995[145]	
Kassem et al., 1975[157]	Zia et al., 1991[146]	
Kondo et al., 1972[140]		

found that fractional addition of ethylcellulose during microencapsulation produced microcapsules which did not rupture during compression[6]. Nontabletted and tabletted microcapsules both exhibited suitable modified release performance.

Gantt et al. produced ethylcellulose microcapsules containing KCl and then applied a PEG-plasticized hypromellose layer onto the microcapsule surfaces[138]. The coated microcapsules were blended with microcrystalline cellulose, cross-linked polyvinylpyrrolidone (PVP) and SLS, and subsequently compressed. Each tablet contained a high dosage (1500 mg) of KCl. The ethylcellulose barrier modulated KCl release, and the hypromellose/PEG layer served as an enhanced binder layer. Rupture of the rate-modulating barrier was minimized using ethylcellulose Std 100 rather than a lower viscosity grade. The hypromellose/PEG-enhanced binder layer allowed a high dosage of microencapsulated KCl to be compressed at low compaction pressure and with minimal amounts of binding excipients, i.e. high-dosage tablets could be produced whereby the majority of the formulation consisted of microencapsulated KCl.

Building upon the findings by Gantt et al., Venkatesh and Kramer produced ethylcellulose microcapsules containing KCl and coated the microcapsules with PEG-plasticized hypromellose[144]. In similar fashion, the microcapsules were formulated with additional excipients and compressed. Ethylcellulose Std 100 was used in order to minimize rupture of the rate-modulating barrier during compression. The PEG-plasticized hypromellose layer served both as an enhanced binder and to facilitate dispersion of the microcapsules upon tablet disintegration. Upon contacting aqueous media, the tablet rapidly disintegrated to individual microcapsules, which then dissipated and released API in modified fashion.

Processability

A total of 6% of the 133 application-based references discuss improved processability via microencapsulation and are listed in Table 5. Improved processability refers to any advancement, which would facilitate downstream dosage form development or packaging, such as improved flowability and compressibility[13,39,137,146,148]. Özyazici et al. studied the effects of microencapsulating nicardipine hydrochloride upon flowability and compressibility[148]. Flowability and compressibility of microcapsules were characterized using angle of repose, Hausner ratio, and the compressibility (Carr) index. The Hausner ratio is determined according to Equation (8).

$$\frac{\text{Density}_{\text{Tapped}}}{\text{Density}_{\text{Bulk}}} \quad (8)$$

The Carr index is determined according to Equation (9).

$$\frac{\text{Density}_{\text{Tapped}} - \text{Density}_{\text{Bulk}}}{\text{Density}_{\text{Tapped}}} \times 100 \quad (9)$$

Table 5. Application-oriented publications where microcapsules were utilized to improve processability. No references were identified where methylcellulose or hypromellose microcapsules were used to improve processability. The references are arranged in similar format to those in Table 1.

Ethylcellulose references
Alpar, 1981[137]
Anderson, 1971[150]
Baichwal and Chidambharam, 1977[168]
Baichwal and Abraham, 1980[12]
Biju et al., 2004[115]
Charle et al., 1973[193]
Farid et al., 1994[210]
Fekete, 1992[211]
Heintz and Teipel, 2000[212]
Morse and Hammes, 1974[171]
Özyazici et al., 1996[148]
Sajeev et al., 2002[39]
Tirkkonen and Paronen, 1993[143]
Tsai and Huang, 1985[13]
Vitek, 1978[213]
Zia et al., 1991[146]

Powder flowability is classified according to specified Carr index and Hausner ratio ranges shown in Table 6[149]. Microencapsulated nicardipine hydrochloride exhibited good and excellent flowability according to the Hausner ratio and Carr index, respectively. Nonencapsulated nicardipine hydrochloride exhibited poor and very poor flowability, respectively. Bulk ethylcellulose exhibited good flowability according to both metrics. Özyazici et al. determined, via scanning electron microscopy, that microencapsulated nicardipine hydrochloride particles were rounder in shape and larger in size compared to nonencapsulated API. Özyazici et al. concluded that microencapsulating nicardipine hydrochloride within ethylcellulose improved API flowability and facilitated both tabletting and filling into capsules without the need for glidant.

Stability

About 9% of the 133 application-based references are listed in Table 7 and report the use of microcapsules to improve API stability[39,95,109,123,150–156]. Cheu et al. produced ethylcellulose microspheres containing acyclovir primarily to modify API release[22]. Cheu et al. also discovered that encapsulation of acyclovir within ethylcellulose

Table 6. Scales of flowability according to compressibility index and Hausner ratio as defined in the USP 33-NF 28[214].

Compressibility index (%)	Flow character	Hausner ratio
10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
> 38	Very, very poor	> 1.60

Table 7. Application-oriented publications where microcapsules were utilized to improve stability. No references were identified where methylcellulose microcapsules were used to improve stability. The references are arranged in similar format to those in Table 1.

Ethylcellulose references		Hypromellose references
Anderson, 1971[150]	Anon., 1974[172]	Ayer et al., 1994[109]
Ayer et al., 1994[109]	Morishita et al., 1985[124]	
Baichwal and Chidambharam, 1977[168]	Morse and Hammes, 1972[170]	
Beatty, 1982[123]	Palomo et al., 1996[158]	
Cedrati et al., 1997[215]	Rani et al., 1994[155]	
Cowsar et al., 1978[191]	Sajeev et al., 2002[39]	
Goto et al., 1973[95]	Sakuma and Atsumi, 1990[160]	
Harte, 1978[152]	Singla and Nagrath, 1988[161]	
Heintz and Teipel, 2000[212]	Szretter and Zakrzewski, 1987[169]	
Kallstrand et al., 1986[153]	Wang et al., 1995[208]	
Kantor et al., 1989[154]	Wang et al., 1996[159]	
Kassem et al., 1975[157]	Yokoyama and Shibata, 1987[156]	

significantly decreased API decomposition upon storage at 37°C and 50°C. In a separate study, Kassem et al. reported that ethylcellulose microcapsules containing L-ascorbic acid were less susceptible to moisture uptake and loss of activity compared to nonencapsulated L-ascorbic acid[157].

Microencapsulation has also been used to protect APIs, which are otherwise unstable at extreme pH conditions, such as those found in the stomach (pH 1-2)[158,159]. Palomo et al. microencapsulated diclofenac sodium within ethylcellulose in order to protect the API from degradation in gastric media[158].

Formulating incompatible ingredients

Microencapsulation has been employed to provide barriers between incompatible ingredients[124,160,161]. Singla and Nagrath produced stable tablets containing both ascorbic acid and zinc sulfate, which was a remarkable achievement because ascorbic acid is oxidized in the presence of zinc sulfate[161]. Ascorbic acid was microencapsulated within ethylcellulose. The microcapsules were then blended with zinc sulfate and various tabletting excipients and subsequently compressed. Microencapsulated ascorbic acid was found to be stable in the presence of zinc sulfate even when the tablets were exposed to elevated temperatures for 80 days.

Taste- or odor-masking

About 6% of the 133 application-based references are listed in Table 8 and discuss the use of microcapsules for taste- or odor-masking. Of the two topics, the majority of references pertain to taste-masking[61,132,136,153,154,162–166]. Taste-masking is often achieved by applying an encapsulating barrier around an API substrate, and the barrier remains intact while the dosage form is administered. Following administration, the barrier allows API release either immediately or in modified fashion.

Four references were identified where taste-masking was achieved because microencapsulated API was released in modified fashion[61,154,163,166]. Golzi et al. produced ethylcellulose microcapsules containing theophylline, and the microcapsules exhibited modified release performance[166]. The microcapsules also exhibited excellent taste-masking properties. Because the API was released slowly, an insufficient amount was released into the mouth to trigger a taste response prior to swallowing.

Kallstrand et al. produced a microcapsule dosage form which could be suspended into water, and release could be delayed until after swallowing the dose[153]. Kallstrand et al. produced ethylcellulose microcapsules containing bacampicillin hydrochloride in a 30:70 barrier:core ratio. Sodium bicarbonate (0.83 g), mannitol (9.35 g), and sucrose (83.1 g) were blended together and then blended with the microcapsules (5.61 g). A 4.81-g aliquot of powder blend was added to 5 mL of water, and API release was measured to be 0.5% after 1 day and 1.2% after 10 days. The suspension was then filtered to isolate the microcapsules, and the microcapsules were diluted with water to mimic volumetric dilution like that which would occur once the microcapsules reached the stomach. Following dilution, API release was 60% and 90% at 1 and 2 h, respectively.

Chewable and orally disintegrating tablets have been formulated primarily for pediatric patients or any patient having difficulty swallowing tablets or capsules. The API is increasingly exposed to saliva as the dosage form is chewed or disintegrated, which often leads to adverse taste. Al-Omran et al. masked the taste of diclofenac sodium in a chewable tablet by encapsulating the API within an ethylcellulose barrier prior to tabletting[136]. The ethylcellulose barrier was applied via either pan-coating or microencapsulation. Chewable tablets formulated with pan-coated API were suitable according to a taste panel, but the API was released immediately upon *in vitro* testing. Chewable tablets formulated with microencapsulated API also produced suitable taste, but microencapsulated API was released in modified fashion. Differences in dissolution performance may have been due to differences in uniformity of the applied ethylcellulose barrier, i.e. a more continuous barrier may have been applied via microencapsulation.

Finally, two references were identified where microencapsulation was used to mask both taste and odor. Alpar

Table 8. Application-oriented publications where microcapsules were utilized for taste- or odor-masking. No references were identified where methylcellulose microcapsules were used for taste- or odor-masking. The references are arranged in similar format to those in Table 1.

Ethylcellulose references		Hypromellose references
Al-Omran et al., 2002[136]	Chikamatsu et al., 1984[164]	Pöllinger et al., 1997[216]
Al-Omran et al., 2002[162]	Chukwu et al., 1991[165]	Pöllinger et al., 1999[217]
Alpar and Walters, 1981[163]	Golzi et al., 2004[166]	Pöllinger et al., 2000[218]
Barzola et al., 2001[132]	Kallstrand et al., 1986[153]	
Beatty, 1982[123]	Kantor et al., 1989[154]	
Becourt et al., 2002[219]	Lavasanifar et al., 1997[61]	

and Walters formulated ethylcellulose microcapsules containing phenethicillin potassium, and the microcapsules masked the taste and almost completely eliminated the objectionable odor of the API[163]. Kantor et al. produced ethylcellulose microcapsules containing fish oil, which is notoriously malodorous and unpalatable, and found that microencapsulation eliminated both taste and odor[154].

Nutraceuticals

About 6% of the application-based references discuss microencapsulation of nutraceuticals. References were identified where nutraceuticals were microencapsulated for various purposes, such as modified release[167], taste-masking[154,164], improved stability[154,161,168,169], nutritional supplementation[141,170,171,172], and animal feed supplementation[152,173]. In particular, several references were identified where vitamin C was microencapsulated to improve its storage stability[157,161,168,169,174,175].

Recall that Kantor et al. produced ethylcellulose microcapsules containing fish oil[154], which is a nutritional supplement known to lower cholesterol, improve circulation, and maintain a healthy heart and brain (see ref. 176). Kantor et al. found microencapsulation beneficial for improving storage stability and eliminating the unpleasant odor and aftertaste of fish oil. Ethylcellulose microcapsules containing fish oil were isolated as a dry powder and could be mixed with various foods for nutritional supplementation.

Nonpharmaceutical applications

Although this review is focused upon pharmaceutical applications, ethylcellulose, methylcellulose, or hypromellose microcapsules are also used for nonpharmaceutical purposes, such as agricultural, dental, printing, clothing, and cosmetic applications.

Agricultural

Agricultural applications for microcapsules include fertilizers[177], herbicides[178–180], pesticides[180,181], and cloud- or fog-seeding agents[150,182]. Anderson[150] and Nelson[182] pioneered research in the early 1970s on cloud- and fog-seeding agents for weather modification. Both Anderson and Nelson encapsulated hygroscopic agents, such as sodium chloride and urea, within ethylcellulose. Controlled particle size and improved storage stability were found to be key attributes of microencapsulated cloud- and fog-seeding agents. Although ethylcellulose acted as a moisture barrier during storage, the ethylcellulose barrier was found to be permeable to moisture at high humidities, which were conditions necessary for cloud- and fog-seeding.

Dental applications

Microcapsules have been used in anticariogenic[160], cariostatic[183], astringent[97], and dental floss[184] applications. For example, Williams et al. formulated ethylcellulose microcapsules containing sodium fluoride and cetylpyridinium chloride[183]. Sodium fluoride strengthens the teeth, and cetylpyridinium chloride kills bacteria that cause plaque and dental caries (see ref. 185). The microcapsules were mixed with powdered guar gum. The blended powder could be sprayed onto the teeth, and the guar gum would hydrate, resulting in adhesion of microcapsules. Sodium fluoride and cetylpyridinium chloride could then be released from the microcapsules in modified fashion. *In vitro* results indicated that this formulation could be used both to increase sodium fluoride uptake into tooth enamel and to provide prolonged oral antiseptic activity.

Printing

As stated in Part 1, microencapsulation originated from printing applications, such as ink toners[186,187] and pressure-sensitive copy paper[188,189]. Witz, for example, used ethylcellulose microcapsules containing aqueous zinc chloride to formulate pressure-sensitive copy paper[189]. Pressure-sensitive copy paper containing these microcapsules produced high-durability color copies of excellent quality.

Clothing

Three references were found where ethylcellulose microcapsules were used in clothing either for wrinkle resistance[190] or for protection from chemical warfare agents[191,192]. For example, Cowsar produced ethylcellulose microcapsules containing decontaminants for mustard blistering agents[192]. Cowsar attached a resin containing the microcapsules to protective clothing fabric. The microcapsules were found to deactivate mustard gas within 1 h.

Cosmetics

Ethylcellulose was used to microencapsulate cosmetic ingredients for nail polish removers[193], antiperspirants/

deodorants[194], and perfumes/insect repellants[195]. Gentilini, for instance, formulated ethylcellulose microcapsules containing tannic acid[194]. Microencapsulated tannic acid was found to modulate perspiration, so the microcapsules were further formulated to produce an antiperspirant/deodorant spray composition.

Review summary

This three-part series represents a comprehensive review of 379 references where ethylcellulose, methylcellulose, or hypromellose was used to make microcapsules. Ingredients needed to formulate microcapsules are discussed in Part 1. Part 2 summarizes the various techniques identified to make microcapsules. Part 3, covered in the current paper, describes the various end-use applications into which microcapsules are utilized. Modified release represents the major end-use application. Hence, it was not unexpected that ethylcellulose was utilized as encapsulating polymer in the majority of the studies. Beyond modified release, many references were identified concerning the use of microcapsules to improve efficacy, safety, processability, and stability as well as to mask unpleasant API taste and/or odor. The various applications have been described in sufficient detail to give the reader a basic understanding of how microcapsules have addressed various industry needs.

Appendix: Continuation of Table 1

Table 1. (continued). Application-oriented publications where microcapsules were utilized to achieve modified release.

Methylcellulose references	Hypromellose references
Cohen, 1986[97]	Ayer et al., 1994[109]
	Gold, 2001[99]
	Hasçiçek et al., 2003[60]

Declaration of interest

The authors are employed by The Dow Chemical Company.

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