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REVIEW ARTICLE

Reviewing the use of ethylcellulose, methylcellulose and hypromellose in microencapsulation. Part 2: Techniques used to make 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 3 of the review are published as separate papers. Part 1 covers the various materials used to formulate microcapsules, and Part 3 covers the various end-use applications for microcapsules. In the current paper, Part 2 covers the techniques used to make microcapsules. Examples of techniques to be covered include temperature-induced phase separation, emulsion solvent evaporation, solvent evaporation, film coating, nonsolvent addition and spray drying. It is hoped that formulators can use Part 2 to understand how to formulate microcapsules using 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, hydroxypropyl methylcellulose, HPMC

Introduction

This review has been developed following evaluation of literature where ethylcellulose, methylcellulose or hypromellose was used to make microcapsules. The review has been divided into 3 major sections. The first section is dedicated to the discussion of various materials used to formulate microcapsules, such as the three encapsulating polymers listed above, protective colloids, plasticizers and surfactants. The second section is focused upon discussion of various techniques used to make microcapsules. The third section is dedicated to discussion of various applications for which microcapsules are used.

A total of 379 references were identified during the literature review. The search methodology utilized to obtain the 379 references is covered in Part 1. Because of the extensive amount of literature identified, this review has been divided into three parts corresponding with the three sections described above. The current paper covers Part 2 of the three-part review. Please refer to Part 1 for a more in-depth introduction.

Microencapsulation techniques

The microencapsulation techniques covered in this review are listed below and are broken down into more commonly and less commonly referenced techniques.

Commonly referenced techniques:

- Temperature-induced phase separation
- Emulsion solvent evaporation
- Solvent evaporation
- Film coating
- Nonsolvent addition

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- Spray drying

Less commonly referenced techniques:

- Complex emulsion
- Emulsion nonsolvent addition
- Simple emulsion
- Emulsion solvent diffusion
- Compressed gas
- Salt addition
- Electrospray

Figure 1 shows a primary analysis of the number of references identified describing each technique and a secondary breakdown of referencing frequency by encapsulating polymer. The most commonly referenced microencapsulation techniques include temperature-induced phase separation (51 references), emulsion solvent evaporation (33 references), solvent evaporation (26 references), film coating (21 references), nonsolvent addition (19 references) and spray drying (13 references). The order of discussion of techniques will progress from most frequently cited to least frequently cited.

It should be noted that microencapsulation techniques have been classified according to the identified primary mechanisms of microcapsule formation. For example, references were classified as temperature-induced phase separation when it was determined that a shift in temperature was utilized to induce phase separation of the encapsulating polymer. It should also be noted that a reference was identified on rare occasion where a combination of techniques was used to formulate microcapsules. For example, Kitakoji et al. formulated multi-walled microcapsules utilizing a combination of emulsification, temperature-induced phase separation, nonsolvent addition and spray drying[1].

Commonly referenced techniques

Temperature-induced phase separation

Temperature-induced phase separation is typically accomplished via reducing the temperature of the encapsulating system in order to induce polymeric coacervation onto a substrate. From Figure 1, it is apparent that ethylcellulose is an encapsulating polymer of choice; all 51 references identified for temperature-induced phase separation communicate the use of ethylcellulose as encapsulating polymer.

References are listed in Table 1 where microcapsules were produced via temperature-induced phase separation. To be concise, one representative example from the literature has been selected to demonstrate this technique. The process used by Samejima et al.[2] is summarized in the flow chart shown in Figure 2. Samejima et al. used ethylcellulose std 100 as encapsulating polymer. Cyclohexane containing polyisobutylene (PIB) and liquid paraffin was heated to 80°C, and ethylcellulose was dissolved into the hot solution. Trimebutine maleate was then dispersed into the hot solution. The dispersion was cooled to 25°C under constant stirring. As the dispersion cooled, the solvation capacity of cyclohexane for ethylcellulose was reduced. Consequently, ethylcellulose was coacervated onto the surfaces of the dispersed active pharmaceutical ingredient (API). The two protective colloids, PIB and liquid paraffin, facilitated coacervation of ethylcellulose and minimized microcapsule aggregation. The newly formed microcapsules were isolated via filtration and subsequently rinsed with hexane. The isolated microcapsules were then dried and sieved to break apart any loose agglomerates.

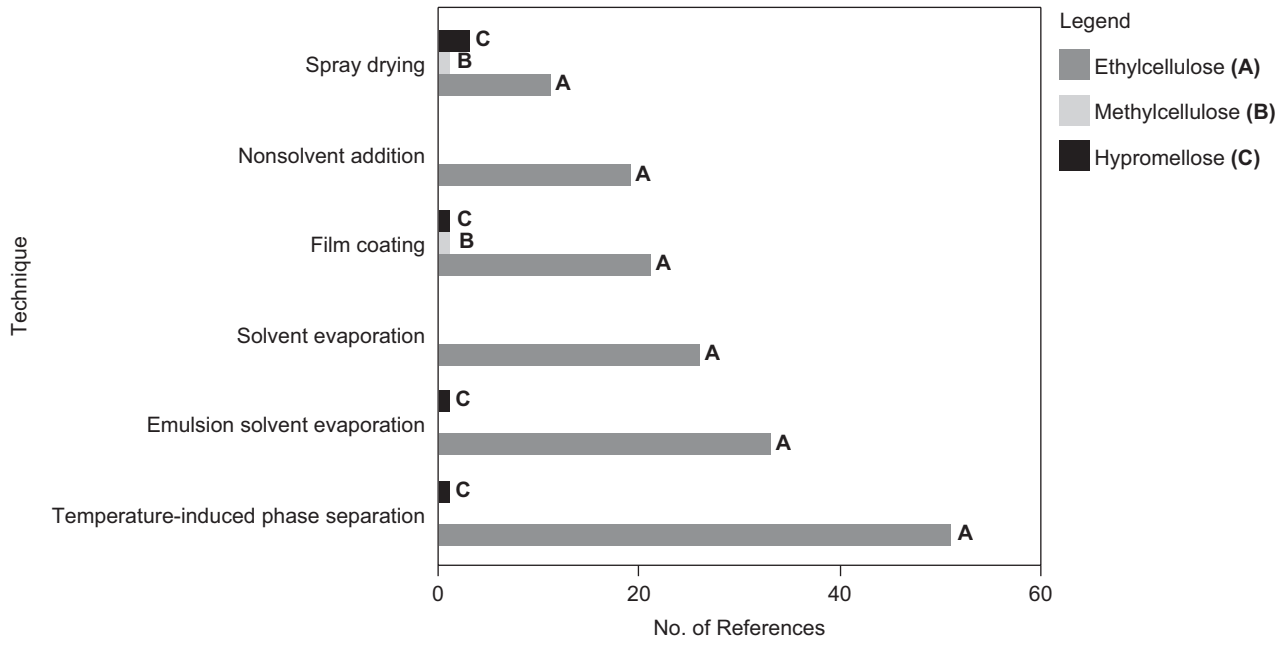

Figure 1. Frequency by which each microencapsulation technique has been referenced in the literature. Referencing frequency is further characterized according to the encapsulating polymer (ethylcellulose, methylcellulose or hypromellose) used to make microcapsules.

Table 1. Process-oriented publications where temperature-induced phase separation was utilized to make microcapsules.

Ethylcellulose references			Hypromellose references
Alam and Eichel[14]	Lin and Yang[15]	Vitkova et al.[16]	Kaltsatos et al.[17]
Alam and Eichel[18]	Lin and Chen[19]	Whitaker Sr[20]	
Anderson et al.[21]	Miller and Anderson[22]	Wieland-Berghausen et al.[23]	
Bettman et al.[24]	Morse[25]		
Calanchi and Gentilini[26]	Morse and Hammes[27]		
Cameroni et al.[28]	Morse et al.[29]		
Carpov et al.[30]	Motycka and Nairn[31]		
Carpov et al.[32]	Nasa and Yadav[33]		
Chemtob et al.[34]	NL 6611661; Anon[35]		
Chemtob et al.[36]	Nixon and Wong[37]		
Deasy et al.[38]	Powell[39]		
Doshi et al.[40]	Rak et al.[41]		
El-Helw[42]	Safwat and El-Shanawany[43]		
Fan et al.[44]	Samejima et al.[45]		
Fekete et al.[46]	Samejima et al.[2]		
Friend et al.[47]	Samejima et al.[48]		
Inoe[49]	Shin and Koh[50]		
John[51]	Singh and Robinson[52]		
Kaltsatos et al.[17]	Singh and Robinson[53]		
Kato[54]	Sveinsson and Kristmundsdottir[55]		
Koida et al.[56]	Szretter and Zakrzewski[57]		
Koida et al.[58]	Uddin et al.[59]		
Kristl et al.[60]	Vitkova et al.[61]		
Lin[62]	Vitkova et al.[63]		

No methylcellulose references were identified where temperature-induced phase separation was used. References are listed alphabetically by the first author's or inventor's last name.

Cyclohexane's altered solvation capacity for ethylcellulose as a function of temperature is exploited in order to produce microcapsules via temperature-induced phase separation. Cyclohexane is a poor solvent for ethylcellulose at ambient temperature. Upon heating, however, cyclohexane has a higher solvation capacity for ethylcellulose. Subsequent cooling results in phase separation and coacervation.

Of the techniques shown in Figure 3, temperature-induced phase separation has most frequently used protective colloids. A variety of protective colloids, such as butyl rubber (4 references), ethylene vinyl acetate (4 references), paraffin (2 references) and silicone (1 reference), have been used during temperature-induced phase separation. Polyethylene (21 references) and PIB (15 references), however, have been used most frequently.

Temperature-induced phase separation is useful for APIs which are insoluble, for example, in cyclohexane. The dispersed API would serve as substrate onto which the coacervated ethylcellulose would be deposited. On the other hand, the microcapsules may not be spherical due to the irregular morphology of the dispersed API. Furthermore, higher barrier:core ratios may be necessary for successful encapsulation of irregularly shaped API substrates.

Emulsion solvent evaporation

Emulsion solvent evaporation was the second-most frequently referenced of the microencapsulation techniques.

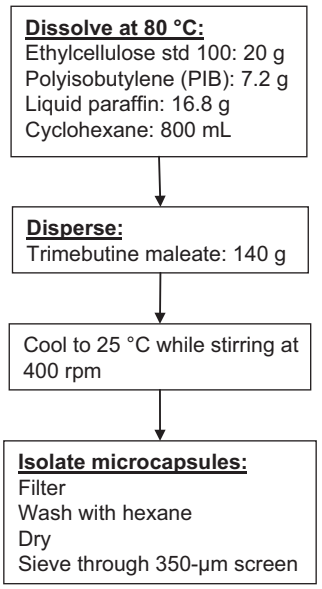

Figure 2. Flowchart depicting the formation of ethylcellulose microcapsules containing trimebutine maleate via temperature-induced phase separation[2].

Table 2 and Figure 1 show that ethylcellulose was used as encapsulating polymer in all 33 references describing emulsion solvent evaporation. Emulsion solvent evaporation is typically accomplished by first forming a simple emulsion. The dispersed phase usually contains API and ethylcellulose, and the continuous phase contains an emulsifier to disperse droplets of the internal phase.

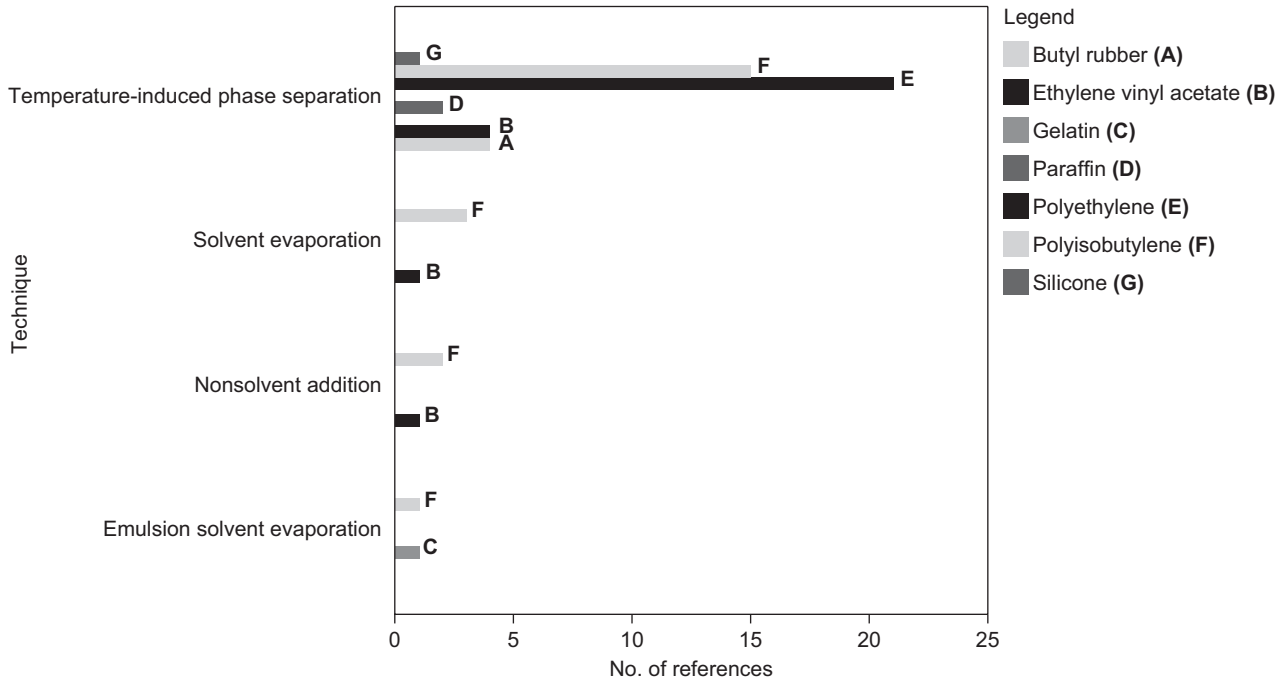

Figure 3. Referencing frequency of each protective colloid according to the microencapsulation technique used.

Table 2. Process-oriented publications where emulsion solvent evaporation was utilized to make microcapsules.

Ethylcellulose references		Hypromellose references
Abu-Izza et al.[64]	Morishita et al.[65]	Guyot and Fawaz[66]
Amperiadou and Georgarakis[3]	Mortada[67]	
Bhalerao et al.[68]	Murthy and Chowdary[69]	
Bodmeier and Chen[70]	Murthy and Chowdary[71]	
Bodmeier and Chen[72]	Perez-Martinez et al.[73]	
Cheu et al.[74]	Ravichandran et al.[75]	
Das[76]	Ruiz et al.[77]	
Elbahri and Taverdet[78]	Sheorey et al.[79]	
Goto et al.[80]	Sriwongjanya and Bodmeier[81]	
Guyot and Fawaz[66]	Uno et al.[82]	
Huang and Ghebre-Sellassie[83]	Wieland-Berghausen et al.[23]	
Jones and Pearce[84]	Yang et al.[85]	
Kentepozidou and Kiparissides[86]	Yang et al.[87]	
Kiritani[88]	Yang et al.[89]	
Lin and Wu[90]	Yang et al.[91]	
Morishita et al.[92]	Zandi et al.[93]	
Morishita et al.[94]		

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

Once the desired emulsion is formulated, the solvent from the dispersed phase is evaporated. Solvent evaporation causes ethylcellulose to phase separate, thus inducing microcapsule formation.

A study published by Amperiadou and Georgarakis[3] has been chosen to illustrate emulsion solvent evaporation, and a flow chart outlining the technique is shown in Figure 4. The dispersed phase consisted of salbutamol sulfate, ethylcellulose and acetone. Ethylcellulose was first dissolved in acetone, and salbutamol sulfate was subsequently suspended into the solution. The continuous phase consisted of light mineral oil containing 1.3% polysorbate 80. The acetonic suspension was dispersed into the mineral oil solution to produce an emulsion. The emulsion was then stirred at 1100 revolutions per min (rpm) at ambient temperature for 5 h in order to evaporate the acetone. As acetone evaporated, ethylcellulose increased in concentration within the dispersed phase and eventually phase separated. Microcapsules were isolated by decanting as much light mineral oil as possible followed by multiple rinses with n-hexane. Finally, microcapsules were isolated via filtration and allowed to air-dry for 12 h.

Although o/w emulsions are often used, Amperiadou and Georgarakis demonstrated that non-aqueous emulsions could be utilized during emulsion solvent evaporation. Using an aqueous continuous phase may prove problematic when encapsulating a hydrophilic API due to the fact that the API might partition into the continuous phase, i.e. encapsulation efficiency would be adversely impacted.

Solvent evaporation

Ethylcellulose was used in all of the 26 references identified for solvent evaporation (see Figure 1 and Table 3). Ethylcellulose is dissolved in an organic solvent or cosolvent mixture. The substrate is added to the organic

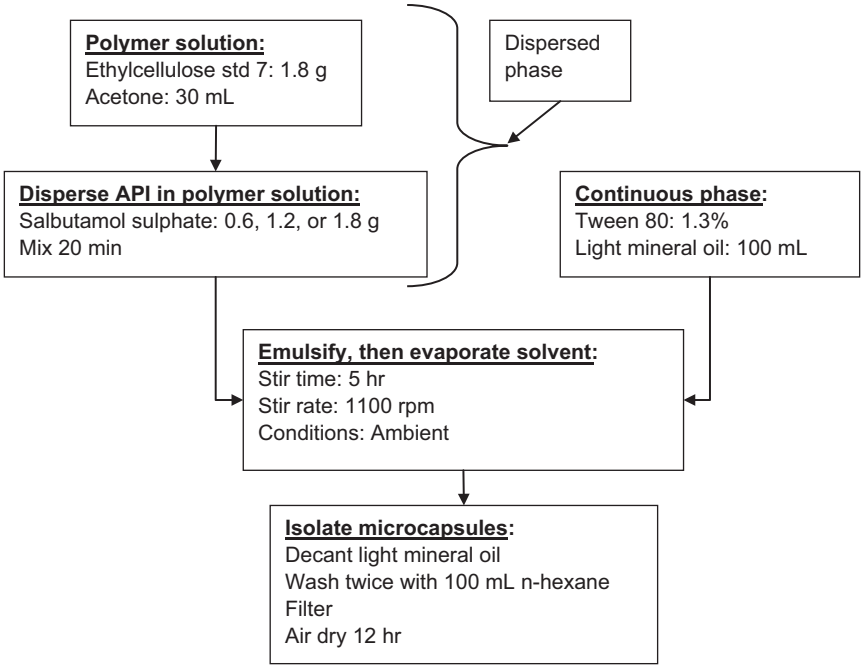

Figure 4. Flowchart depicting the formation of ethylcellulose microcapsules containing salbutamol sulfate via emulsion solvent evaporation[3].

Table 3. Process-oriented publications where solvent evaporation was utilized to make microcapsules.

Ethylcellulose references	
Andre-Abrant et al.[95]	Manekar et al.[96]
Arabi et al.[97]	Manekar et al.[98]
Assimopoulou and Papageorgiou[99]	Moldenhauer and Nairn[4]
Cristallini et al.[100]	Moldenhauer and Nairn[101]
Dubernet et al.[102]	Moldenhauer and Nairn[103]
Elbary et al.[104]	Rhee et al.[105]
Ghorab et al.[106]	Sarin et al.[107]
Ibrahim et al.[108]	Tsujiyama et al.[109]
Khalil and El-Gamal[110]	Uchida et al.[111]
Kosenko et al.[112]	Uchida et al.[113]
Kristmundsdottir and Ingvarsdottir[114]	Uddin et al.[59]
Ku and Kang[115]	Yoshida[116]
Manekar et al.[117]	Zhu et al.[118]

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

solution and the solvent is evaporated. As solvent evaporates, its solvation capacity for ethylcellulose is reduced. The concentration of dissolved ethylcellulose increases to a critical point at which ethylcellulose phase separates and coacervates onto the surfaces of the substrates. Further solvent evaporation drives coacervation to completion.

Moldenhauer and Nairn[4] produced microcapsules using the process illustrated in Figure 5. PIB was dissolved in cyclohexane. A theophylline/ion-exchange resin complex was suspended into the cyclohexane solution and mixed for 20 min. Next, light liquid paraffin was added as a nonsolvent. In a separate step, ethylcellulose was dissolved in ethyl acetate. The solution containing ethylcellulose was added to the cyclohexane suspension containing the API-resin complex. The mixture was then stirred under a continuous purge of air to evaporate cyclohexane and ethyl acetate. Solvent evaporation rate was varied by adjusting the diameter of the hole through which solvent vapor and purge air escaped from the mixing vessel. Solvent evaporation led to phase separation and coacervation of ethylcellulose onto the API-resin complex. The resulting microcapsule suspension was diluted with 100 mL of cyclohexane while continuously stirring. The microcapsules were isolated via filtration, washed four times with 75 mL of cyclohexane, and dried.

Solvent evaporation is beneficial when encapsulating a water-soluble API. However, the microcapsules may not be spherical due to the irregular morphology of the dispersed API. Furthermore, higher barrier:core ratios may be necessary for successful encapsulation of irregularly shaped API substrates.

Film coating

Ethylcellulose was used in all 21 references identified for film coating, as shown in Table 4 and Figure 1. Although barrier-coated multiparticulates may not fall within the micron size range, several references were found where microcapsules were produced via film coating. Formulation of microcapsules via film coating is typically performed in a fluidized bed by applying a coating onto powders, beads, granules or pellets. Fluidization facilitates application of a uniform coating onto each particle.

Figure 6 schematically illustrates an example where Lippold et al. utilized film coating to make microcapsules[5]. Lippold et al. first formulated pellets containing guaiphenesin, Avicel PH-101 (FMC BioPolymer) and Kollidon K90 (BASF) via extrusion-spheronization. Pellet

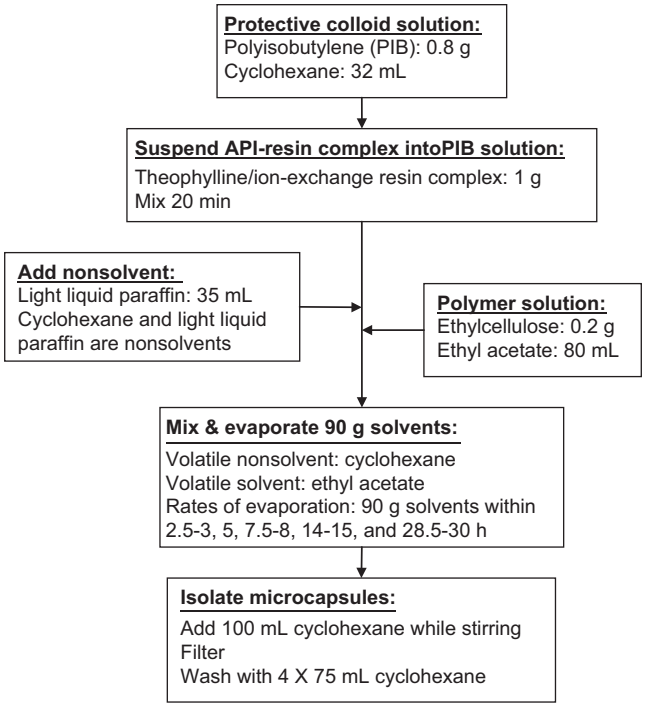

Figure 5. Flowchart depicting the formation, via solvent evaporation, of ethylcellulose microcapsules containing a theophylline/ion-exchange resin complex[4].

sizes ranged from 1 to 1.25 mm. The pellets were charged into an Aeromatic Strea-1 fluidized bed chamber (Niro Pharma Systems , Switzerland), fluidized and equilibrated using the conditions listed in Figure 6. Once equilibrated, the pellets were encapsulated within ethylcellulose by spraying Aquacoat ECD, an aqueous dispersion containing ethylcellulose pseudolatex, onto the pellets. Aquacoat ECD was applied until a solid weight gain of 13.9–15.3% was attained. After the desired solid weight gain had been attained, the Aquacoat ECD feed was stopped, and the microencapsulated pellets were fluidized for an additional 5 min. The microencapsulated pellets were then collected and thermally post-treated for 1 h at 40, 50 or 68°C.

Some might argue that film coating is a preferred technique because encapsulation efficiency is essentially 100%. In addition, this type of encapsulation employs common fluidized bed equipment and could be achieved without the use of solvents. In contrast, some might argue that barrier-coated multiparticulates are not microcapsules because multiparticulates are typically in the millimeter size range.

Nonsolvent addition

Nonsolvent addition occurs when an antisolvent or nonsolvent is added to a polymeric solution resulting in phase separation. The nonsolvent typically reduces solvation capacity of a solvent by reducing the degree of molecular interaction between the solvent and the dissolved encapsulating polymer. Reduced solvation capacity causes the polymer to phase separate and subsequently coacervate onto substrate surfaces.

Table 4. Process-oriented publications where film coating was utilized to make microcapsules.

Ethylcellulose references	Methylcellulose references	Hypromellose references
Becourt et al.[119]	Zulkarnain[120]	Zulkarnain[120]
Becourt et al.[121]		
Bruschi et al.[122]		
Calanchi and Gentilini[26]		
Cordes[123]		
Elbary et al.[104]		
Fukumori et al.[124]		
Fukumori et al.[125]		
Giannini and Bashour[126]		
Han and Li[127]		
Ichikawa and Fukumori[128]		
Kassem et al.[129]		
Kim et al.[130]		
Knezevic et al.[131]		
Lippold et al.[5]		
Persson and Lindblom[132]		
Rhee et al.[105]		
Senjkovic and Jalsenjak[133]		
Snipes and Wagner[134]		
Wieland-Berghausen et al.[23]		
Zulkarnain[120]		

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

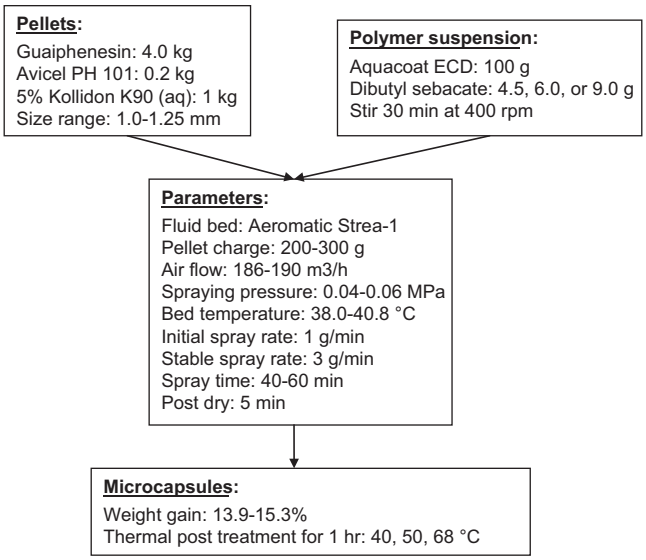

Figure 6. Flowchart depicting the formation of ethylcellulose microcapsules containing guaiphenesin via film coating in a fluidized bed[5].

As shown in Table 5 and Figure 1, ethylcellulose was used in all of the 19 references identified for nonsolvent addition. For example, D'Onofrio et al. used nonsolvent addition to formulate ethylcellulose microcapsules containing aspirin[6]. Four to ten grams of ethylcellulose were slowly added and dissolved in 600 mL of ethyl acetate while continuously stirring at 80 rpm. Next, 350 mL of light liquid paraffin were added to prime the system for coacervation of ethylcellulose; and the agitation speed was increased to 1500 rpm. Thirty minutes later, 40.0 g

Table 5. Process-oriented publications where nonsolvent addition was utilized to make microcapsules.

Ethylcellulose references	
Al-Omran et al.[135]	Motycka and Nairn[31]
Barik et al.[136]	Nixon and Meleka[137]
Barik et al.[138]	Nixon and Nimmannit[139]
D'Onofrio et al.[6]	Nixon and Wong[37]
El-Helw and Bayomi[140]	Salib et al.[141]
Itoh et al.[142]	Wu et al.[143]
Khalil and El-Gamal[110]	Wu et al.[144]
Khanna et al.[145]	Yazici et al.[146]
Moldenhauer and Nairn[101]	Zhang et al.[147]
Moldenhauer and Nairn[103]	

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

Table 6. Process-oriented publications where spray drying was utilized to make microcapsules.

Ethylcellulose references	Methylcellulose references	Hypromellose references
Forni et al.[148]	Du et al.[149]	Lin et al.[150]
JP 58035111 A2; Anon[151]		Du et al.[149]
Kitakoji et al.[1]		Wan et al.[152]
Liao et al.[153]		
Lin et al.[150]		
Mao and Zhang[154]		
Sfar and Karoui[155]		
Uddin et al.[59]		
Vo et al.[156]		
Yamada et al.[157]		
Zhang et al.[158]		

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

of aspirin were added and allowed to disperse homogeneously throughout the solution. Sixty minutes after adding aspirin, two additional liters of light liquid paraffin were added, and the system was stirred for 60 min to allow coacervation of ethylcellulose to complete. Finally, stirring was stopped; the microcapsules were allowed to settle overnight; and excess light liquid paraffin was removed via decantation. The concentrated microcapsule slurry was then filled into soft gelatin capsules and further investigated.

Nonsolvent addition might prove beneficial if the API were insoluble in the both the solvent and nonsolvent, but higher barrier:core ratios might be necessary to completely encapsulate irregularly shaped surfaces of dispersed API particles. API migration (i.e. low encapsulation efficiency) would be a challenge if the API were soluble in the solvent, the nonsolvent, or the mixture. Referring to the example above, isolation of dry microcapsule powder from light liquid paraffin would be a challenge due to paraffin's low vapor pressure and poor solubility in relatively eco-friendly solvents, like ethanol.

Spray drying

References are listed in Table 6 where spray drying was used to produce microcapsules or microspheres.

Table 7. Process-oriented publications where complex or simple emulsion, emulsion nonsolvent addition, or emulsion solvent diffusion techniques were utilized to make microcapsules.

Ethylcellulose references	Methylcellulose references	Hypromellose references
Complex emulsion	Complex emulsion	Complex emulsion
Chowdary and Babu[159]	Chowdary and Ratna[160]	Du et al.[149]
Chowdary and Ratna[160]	Du et al.[149]	
Das[76]		
Du et al.[149]		
Jani et al.[161]		
Kentepozidou and Kiparissides[86]		
Morris and Warburton[162]		
Rao et al.[8]		
Sriwongjanya and Bodmeier[81]		
Yoshida et al.[163]		
Zhang[164]		
Emulsion nonsolvent addition		
Chen et al.[165]		
Chen et al.[166]		
Chowdary and Rao[167]		
Chowdary and Nageswara Rao[168]		
Chowdary and Rao[169]		
Kaeser-Liard et al.[170]		
Kitakoji et al.[1]		
Yang et al.[85]		
Yang et al.[87]		
Simple emulsion		
Chan and Heng[171]		
Chow et al.[10]		
Salib et al.[172]		
Whitaker Sr[20]		
Emulsion solvent diffusion		
Mallick et al.[173]		
Rao et al.[8]		

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

Ethylcellulose was used in 11 of those 13 references, but methylcellulose and hypromellose have also been used. For example, Hascicek et al. utilized spray drying to formulate hypromellose microspheres containing gentamicin sulfate[7]. The microspheres were designed to facilitate systemic absorption of the highly polar API by forming mucoadhesive multiparticulates upon contact with the nasal mucousa. A 1% (w/v) polymer solution was prepared by adding hypromellose to distilled water while stirring at room temperature. Next, a sufficient amount of gentamicin sulfate was dissolved into the solution to obtain a 1:4, 1:2, 1:1 or 2:1 weight ratio (hypromellose:API). Finally, sodium cholate was added to the solution at a concentration of 1% (w/w) relative to the total amount of hypromellose and gentamicin sulfate. While continuously stirring, the solution was sprayed through a 0.7-mm diameter nozzle into a spray dryer (Type 190, BÜCHI Labortechnik

AG, Switzerland). Inlet and outlet temperatures were equilibrated to 150–155 and 95–97°C, respectively. The aspirator setting was adjusted to 10, and the spray pump was set to deliver solution at 2–5 mL/min. The air flow was adjusted to 700 N l/h. Microspheres were collected and kept under vacuum for 24 h prior to analysis.

It should be noted that a microcapsule is generally regarded as an API core encapsulated within a thin polymeric barrier coating, whereas a microsphere is regarded as a spherical matrix consisting of API and polymer blended throughout the particle. According to these definitions, spray drying typically produces microspheres instead of microcapsules.

Some may consider the balloon-like low-density or monolithic nature of microspheres disadvantageous. As Hascicek et al. did, in addition, a vacuum drying post-processing step might be necessary to minimize residual solvent. The simplicity and prevalence of spray drying may, however, counter-balance perceived disadvantages. Furthermore, solutions and dispersions are both easily processed via spray drying; but one must use caution to prevent settling of dispersions.

Less commonly referenced techniques

Less commonly referenced microencapsulation techniques include complex emulsion (11 references), emulsion nonsolvent addition (9 references), simple emulsion (4 references), emulsion solvent diffusion (2 references), compressed gas (3 references) and salt addition (2 references). References for these techniques are listed in Table 7.

Complex emulsion

Rama Rao et al. produced ethylcellulose microcapsules containing zidovudine using a water-in-oil-in-oil (w/o/o) complex emulsion solvent diffusion method[8]. (Note that this process was actually a hybrid of two microencapsulation techniques: complex emulsion and emulsion solvent diffusion.) Acetonitrile and dichloromethane (50:50) made up the intermediate oil phase. Ethylcellulose (300 mg) and zidovudine (150 mg) were both dissolved in 5 mL of the intermediate oil phase. Two milliliters of water were added to the intermediate oil phase and stirred at 500 rpm for 5 min to make the primary w/o emulsion. Ethylcellulose served a secondary role as emulsion stabilizer. The primary w/o emulsion was added to 50 mL of light liquid paraffin containing 0.5% Span 80 while stirring at 1000 rpm. The resulting w/o/o emulsion was stirred for 2 h. During this timeframe, acetonitrile and dichloromethane diffused from the intermediate oil phase into the continuous oil phase to initiate phase separation of ethylcellulose and zidovudine. Ten milliliters of n-hexane were added to harden the microspheres, and the system was stirred for an additional hour. The hardened microspheres were isolated via filtration, washed with three 50-mL portions of n-hexane and air-dried for 12 h.

Rama Rao et al. cited several studies where zidovudine undesirably diffused from the organic phase into the aqueous phase, which diminished encapsulation efficiency. Hence, Rama Rao et al. used an internal water phase in order to maximize retention of zidovudine inside the microcapsule core.

Complex emulsions are challenging because multiple emulsification steps are necessary. For example, the first emulsification step should result in a primary emulsion containing very small internal phase droplets. The secondary emulsion is often made using gentler agitation conditions, which will result in larger secondary phase droplets still containing the very small internal phase droplets. The secondary phase droplets, themselves, will be dispersed in the continuous phase. One must ensure that droplet sizes in each phase can be produced consistently from batch-to-batch. Complex emulsions are beneficial, however, because they produce spherical, compartmentalized microcapsules, which could be used to formulate incompatible ingredients.

Emulsion nonsolvent addition

Emulsion nonsolvent addition involves production of an emulsion followed by addition of a nonsolvent to produce microcapsules. For example, Witz formulated microcapsules for pressure-sensitive copy paper by forming a water-in-oil (w/o) emulsion and subsequently adding silicone oil as nonsolvent[9]. (Note that this example describes a printing application.) An aqueous saturated solution containing zinc chloride (solution pH 4.6) was dispersed at room temperature in toluene containing 6% ethylcellulose. Next, silicone oil was added drop-wise to induce microcapsule formation. The microcapsules were then isolated by decantation, washed, dried and subsequently used to make pressure-sensitive copy paper.

Emulsion nonsolvent addition would offer similar benefits and challenges to those described earlier regarding nonsolvent addition.

Simple emulsion

Chow et al. produced ethylcellulose microcapsules from o/w emulsions[10]. Either of two cosolvent systems served as the dispersed oil phase: (i) dichloromethane and cyclohexane (40:60 v/v) or (ii) dichloromethane and hexane (50:50). These cosolvent systems were chosen to match the density of the aqueous continuous phase. One to three grams of ethylcellulose std 7 were dissolved in 40 mL of either cosolvent system. The continuous phase consisted of a saturated solution of cefaclor monohydrate in water in order to minimize API migration from the dispersed phase into the continuous phase. Cefaclor monohydrate (250–355 μm particle size) and polyvinylpyrrolidone 40 k (1.2 g) were dispersed into the cosolvent system at levels necessary to achieve ethylcellulose:API weight ratios of 1:2, 2:2, 3:2, 2:1 or 2:3. The oil phase was then added to the aqueous phase in a 1-L reaction vessel at 20 ± 1°C while stirring at 700–900 rpm. The emulsion was stirred

overnight, and the resulting microcapsules were filtered and oven-dried at 40°C for 48 h.

As noted by Chow et al., o/w emulsions are challenging because a hydrophilic API may migrate into the continuous phase. In addition, there should be steps for removing organic solvents and inducing coacervation. These challenges are manageable, and concerns over batch-to-batch consistency are not as high as those regarding complex emulsions.

Emulsion solvent diffusion

In the study discussed earlier, Rama Rao et al. used dichloromethane as part of the cosolvent system forming the intermediate oil phase because it is a nonpolar, oil-miscible solvent[8]. During the 2-h stirring period, dichloromethane diffused from the intermediate oil phase into the liquid paraffin continuous phase. Diffusion of dichloromethane facilitated phase separation of microspheres exhibiting improved encapsulation efficiency and exceptional modified release performance.

Emulsion solvent diffusion is utilized most effectively when neither the API nor the encapsulating polymer is soluble in the continuous phase. Otherwise, low encapsulation efficiency would be a significant limitation. Emulsion solvent diffusion is comparable to emulsion solvent evaporation in that microencapsulation occurs when solvent capacity is reduced, resulting in phase separation. While solvent escapes via emulsion solvent evaporation, however, solvent remains present in the system following emulsion solvent diffusion.

Compressed gas

Zhang et al. produced ethylcellulose microcapsules via supercritical carbon dioxide (CO_2) antisolvent precipitation (SAS[11]). Ethylcellulose was dissolved in acetone at a concentration ranging from 1 to 5.5% (w/v). The solution was then introduced into a high-pressure precipitation chamber and agitated using a magnetic stir bar rotating at a rate set between 16 and 55 rpm. The precipitation chamber was completely submerged in water equilibrated to a set temperature ranging from ambient to 100°C, and the acetonic solution was allowed to equilibrate to set temperature in each case. Next, CO_2 was metered into the chamber until the desired pressure was attained. At no time was the chamber pressurized above 50 MPa. Back-pressure regulators on the precipitation and separation chambers stabilized pressure and allowed CO_2 to be continuously replenished. Continuous CO_2 replenishment facilitated acetone removal from the ethylcellulose microcapsules. The flow of CO_2 was finally stopped, and the chamber was vented to atmospheric pressure in order to harvest the ethylcellulose microcapsules. Ethylcellulose microcapsules exhibited diameters ranging from 2.66 to 9.49 µm. Larger microcapsules were produced with higher temperatures and solution concentrations. Smaller microcapsules were produced with higher pressures and agitation rates.

Organic solvents often have high affinities for supercritical CO_2 so residual solvents are of less concern. In our experience, low product yields and high processing pressures continue to be challenges.

Salt addition

Salt addition follows a similar mechanism for microencapsulation to that of nonsolvent addition. The encapsulating polymer is dissolved in a solvent, which also contains a substrate to be encapsulated. A salt is added which causes the polymer to phase separate and coacervate onto the substrate surfaces. Yalabik-Kas disclosed a method whereby ethylcellulose microcapsules containing oxazepam (1:1 or 2:1 barrier:core ratio) were produced via salt addition[12]. A solution of ethylcellulose in methylethylketone was stirred at 680 rpm and equilibrated to 50°C in a 1-L three-necked flask. Oxazepam was dispersed into the solution. A 10% disodium hydrogen phosphate salt solution was added over 60 min from a separatory funnel. The mixture was then stirred for an additional 60 min followed by rapidly cooling in an ice bath to room temperature. The hardened ethylcellulose microcapsules were decanted and washed with water three times to remove residual salt. The microcapsules were filtered and air-dried.

Residual salt levels present a concern, so multiple rinses are often employed. One must use caution, on the other hand, to minimize API loss during rinsing.

Electrospray

A combination of ethylcellulose and stearic acid was employed to make solid lipid micro- and nanoparticles containing tamoxifen. Trotta et al.[13] evaluated the utility of a novel electrohydrodynamic—or electrospray—atomization technique for making the lipid particles. The authors successfully made monodisperse, submicron solid lipid particles using a stearic acid:ethylcellulose ratio of 4.5:0.5 (w/w). Although an initial burst in release occurred, the authors observed suitable modified release performance afterwards and concluded that encapsulation efficiency was satisfactory. Trotta et al. proposed utility of electrospray for one-step production of solid lipid micro- and nanoparticulate powders for drug delivery.

Review summary

This three-part series represents a comprehensive review of 379 references where ethylcellulose, methylcellulose or hypromellose was used to make microcapsules. The various ingredients needed to formulate microcapsules are discussed in Part 1, which is covered in a separate paper. Part 3, covered in a third paper, discusses the various end-use applications for microcapsules. Part 2, covered in the current paper, discusses the various techniques employed to make microcapsules. The various techniques have been described in sufficient detail to give the reader a basic understanding of how microcapsules

are made as well as the benefits and challenges of each technique.

Declaration of interest

The authors are employed by The Dow Chemical Company.

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