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ETHYLCELLULOSE MICROPARTICLES: A REVIEW

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Abstract: Ethylcellulose (EC) based microencapsulated drug delivery systems are being extensively studied throughout the world for achieving extended drug release and protecting the core substance from degradation. The *in vitro* evaluation of EC microcapsules have elucidated that their particle characteristics are very useful to control drug release behavior, since these enable drugs to be released at a certain controlled release rate based on the characteristics of drug-EC linkage. This review encompasses microencapsulation techniques, core substances and other fundamentals involved in the preparation and characterization of EC microcapsules. EC microcapsules can be considered as mini-osmotic pumps. The release kinetics for EC microcapsules can be fine-tuned by altering osmolality of the dissolution medium or formulations and EC film mechanical characteristics by selecting appropriate EC molecular weights (viscosity), EC substitution grades, coating weights, and pore formers.

Keywords: ethylcellulose, microparticles, extended release, *in vitro* behavior

Microparticulate formulations

Throughout the world, continuous efforts are in progress for developing improved, optimized and advanced drug delivery systems. Pharmaceutical technologists, biotechnologists, bioengineers and biophysicists are actively imparting their capabilities in the enthusiastic interdisciplinary research activities for the formulation of efficacious drugs (1). Recently, exhaustive research has been made on the microfabrication of polymeric particles, named as microencapsulation and the resulting formulations are expressed as microparticles, microcapsules or microspheres. The term microparticles represents drug containing solid, liquid or gaseous cores completely surrounded by continuous porous or non-porous polymeric shells, whereas the microspheres indicate homogeneous solution or dispersion of drug in solid polymeric matrix. Large research is made to evaluate physicochemical characteristics of microparticles particularly release behavior under *in vitro* and *in vivo* conditions. The microparticles are administered largely after tabletting or filling into hard gelatin capsules or by injection. The performance of multi-unit coated microparticles is considered better than single unit matrix tablets for controlled delivery of high dose and highly soluble drugs (1).

Reasons of microencapsulation

A substance may be microencapsulated for a number of reasons, which can be described in detail as given below (2):

1. To develop modified release dosage forms for targeted or sustained release purpose.
2. To mask the taste of bitter or noxious drugs for their convenient handling.
3. For converting volatile and oily substances or extracts to tabletted dosage forms to avoid tacky granulations and improve flow properties.
4. To protect drugs from environmental hazards such as humidity, light, oxygen or heat and gastrointestinal biodegradation.
5. To enhance compatibility between various drugs and excipients formulated together.
6. For easy handling of hygroscopic and toxic substances such as fumigants, herbicides, insecticides and pesticides.
7. To prepare immobilized cells or enzymes.

Encapsulating materials

The physicochemical characteristics of resulting microparticles depend essentially upon the nature of encapsulating materials. The encapsulating material should be stable and inert to core and excipients, non-hygroscopic and capable of producing a

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cohesive film with the core substance. It should impart the desired coating properties such as strength, brittleness, flexibility, impermeability, optical properties and stability. It should be soluble in an aqueous media or solvent, or melting and capable of controlling drug release. Various encapsulating materials used in microencapsulation are vegetable gums, celluloses, condensation polymers, homopolymers, copolymers, proteins and curable polymers (2).

Among these, celluloses are the largest polymer family that has most extensively been employed in microencapsulation. On the basis of solubility, cellulose polymers are of two types:

1. Hydrophilic cellulose polymers such as hydroxypropyl methylcellulose (HPMC).
2. Hydrophobic cellulose polymers such as ethylcellulose (EC).

Ethylcellulose

EC is a derivative of cellulose in which some of the hydroxyl groups on the repeating anhydroglucose units are modified into ethyl ether groups, largely called as non-ionic ethyl ether of cellulose (Fig. 1) (3).

EC has extensively been used for microencapsulation due to its many versatile properties such as (4): 1. white to light tan odorless and tasteless powder or granular substance; 2. melting point range 240–255˚C; 3. specific density range 1.07–1.18 with 135–155˚C heat distortion point and 330–360˚C fire point; 4. water insoluble but soluble in many organic solvents such as alcohol, ether, ketone and ester; 5. biocompatible and compatible with many celluloses, resin and almost all plasticizers; 6. non-biodegradable, thus used in oral formulation only; 7. stable against light, heat, oxygen and wetness and chemicals; 8. non-toxic; 9. non-irritant; 10. tablet binder to impart plastic flow properties to particles; 11. ability to absorb pressure and hence protect the coating from fracture during compression. Its thin film exhibits good flexibility and mechanical strength in a wide range of temperature (5); 12. non-swellable and water insoluble, thus EC compactness and porosity plays key role in drug release from such hydrophobic materials (6); 13. although EC is water insoluble, it can take up water. This is owing to its hydrogen bonding potential with water attributable to the polarity difference between the oxygen atom and the ethyl group of EC (6, 7); 14. EC, like other hydrophobic polymers used in drug delivery systems, does not require the addition of release modifiers. These additives craft channels in polymer matrix through which drug diffuses out or enhance the wettness of the hydrophobic polymer matrix (6); 15. based on ethoxy contents (%), there are three classes of EC such as K, N and T type, which contain 44–47.9%, 48–49.5% and 49.6–51.0% ethoxy contents, respectively. Based on chain length or degree of polymerization or the number of anhydroglucose units, EC is available as a number of different viscosity grades. The apparent viscosity of the polymer can be regarded as an indirect measure of its molecular weight (4).

Applications of EC

EC is used for microencapsulation of various pharmaceuticals to stabilize them against active interactions, hydrolysis and oxidation. It also is employed as a matrix and/or coating agent to impart sustained release characteristics. However, the selection of a suitable polymer and development of microcapsules is a time consuming and complex process, which requires complete command over the in-depth knowledge of physico-chemical properties of various drugs and polymers. This review narrates the fundamentals of using EC for the development of its multiparticulates.

EC microparticles can be considered as mini-osmotic pumps (8). The release kinetics for EC microparticles can be fine-tuned by altering osmolality of the dissolution medium or formulations and

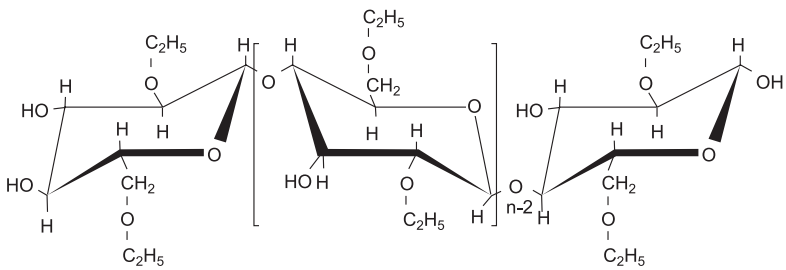

Figure 1. Structural formula of EC

EC film mechanical characteristics by selecting appropriate EC molecular weights, EC substitution grades, coating weights, and pore formers. The release of a highly or sparingly soluble drug from a dosage from is considerably reduced when osmolality of the dissolution medium is increased causing a reduction in osmotic pressure gradient across the release controlling membrane (8, 9). Drug release rates are drastically reduced with the increase in EC molecular weight. According to a general concept, polymer chain length increases with the increase in its molecular weight, resulting in stronger film with increased tensile strength and elasticity. It comes into view that the stronger films may resist hydrostatic pressure, ensuring less structural damage to the film due to stress fractures or channel formation. It has been elaborated that formulations coated with lower molecular weight had faster release rates as compared to the formulations coated with higher molecular weight EC (8).

The release of a drug from high ethoxyl T10 EC formulation is considerably increased as compared to intermediate ethoxyl N10 EC. According to a general concept, EC film tensile strength decreases with the increase in ethoxyl contents (%) resulting in the high release rate. EC molecular weight and ethoxyl contents can thus be utilized to alter film permeability characteristics and ultimately release behavior (8). In addition, selection of suitable EC grade can be made in accordance with the solubility of drug. For highly soluble drugs or formulations with high osmolality, higher molecular weight intermediate ethoxyl contents (%) EC such as EC N22 should be preferred. However, coating weight and addition of a suitable pore former/plasticizer should also be considered. For low solubility drugs, increased membrane permeability is needed. Therefore, low molecular weight intermediate ethoxyl grades such as EC N10 or high ethoxyl contents (%) such as EC T10 can be used with lower coating weights i.e., use of low EC concentration. It has been observed that there is an increase in solution viscosity with the increase in the molecular weight of EC or its coating weight, resulting in the immobilization of solvated polymer molecules. In short, selection of appropriate grade of EC regarding its molecular weight or viscosity and its concentration used is necessary to achieve desired drug release profile (8, 10).

It has been presented previously (10) that EC having short chains produced comparatively weaker films. Hence, the mechanical properties of polymer coating improve with the increase in molecular weight. This statement is true for a specific range of EC molecular weights beyond which there is no improvement in the membrane strength. Similar influence was also noted in the comparison of dissolution data obtained from formulations with different viscosity grades of EC. Drug release was the slowest when high viscosity EC (45 cP) was employed, while the formulations with low viscosity grade EC (4 cP) released drug at the fastest rate. Similar results have also been presented in another study where the researchers have used three different viscosity grades of ethylcellulose i.e., 10 cp, 22 cp and 46 cp (11). Murtaza et al. (11) and Row (12, 13) have elaborated the influence of molecular weight and mechanical properties of EC on release behavior. These studies also confirmed the theory of fracturing of polymer film prepared with low molecular weight EC. The fracturing property decreases with an increase in EC molecular weight.

The *in vitro* data indicated that mechanical properties of EC films can be improved with the increase in molecular weight and by the addition of plasticizers (13). The addition of plasticizer reduces the internal stress of coating, making the film sounder. In a previous study, EC Standard 10 Premium films were prepared using various quantities of plasticizer. It was found that drug release slowed down with an increase in the amount of plasticizer used. Such a result can be attributed to a sounder EC film produced as a result of reduced internal stress of coating. Addition of plasticizer improves the flexibility of the polymer chains and produces a less porous network. It exerts its influence by interposing between the polymer chains, thus decreasing cohesion between the polymer. This converts the hard brittle shell to one that is flexible and tough (13, 14).

Techniques employed for the preparation of EC microparticles

EC microparticles have been formulated using a variety of techniques. However, many techniques of microencapsulation have common characteristics. The microencapsulation techniques can be classified as given below (15):

1. Chemical processes such as interfacial and in-situ polymerization methods.
2. Physiochemical processes such as coacervation-phase separation and complex emulsion.
3. Electrostatic processes.
4. Mechanical processes such as air-suspension method, pan coating and spray drying, spray congealing, micro-orifice system and rotary fluidization bed granulator method.

Table 1. Microencapsulation of various drugs using single polymer.

No.	Drug	Water solubility	Formulation	Technique employed	Reference
1	DS	Sparingly soluble	ER	SE	37
2	DS	Sparingly soluble	Taste masking	SE	38
3	DS	Sparingly soluble	ER	Coacervation	39
4	DS	Sparingly soluble	ER	SE	40
5	DS	Sparingly soluble	ER	Coacervation	41
6	DS	Sparingly soluble	ER	Coacervation	42
7	DS	Sparingly soluble	ER	Coacervation	28
8	DS	Sparingly soluble	ER	SE	43
9	SS	Readily soluble	ER	Coacervation	44
10	SS	Readily soluble	ER	SE	45
11	SS	Readily soluble	To study effect of surfactant	SE	46
12	SS	Readily soluble	ER	Three techniques	29
13	TH	Freely soluble	ER	Coacervation	34
14	TH	Freely soluble	ER	Spray drying	47
15	TH	Freely soluble	CR	Coacervation	3
16	Ranitidine HCl	Soluble	CR	SE	48
17	Tolmetin sodium	Soluble	MR	Emulsion solvent diffusion	49
18	Nimesulide	Insoluble	ER	Desolvation method	50
19	Nimesulide	Insoluble	ER and photo-degradation	Modified SE	51
20	Diltiazem HCl	Soluble	Nasal drug delivery	Modified ESE	52
21	Aspirin	Insoluble	MR	SE	53
22	Aspirin	Insoluble	ER/Simulation study	SE	54
23	Nifedipine	Insoluble	ER	SE	55
24	Cefadroxil and Cephradine	Insoluble	ER	SE	56
25	Indomethacin and Ascorbic acid	Soluble	ER	Coacervation	57
26	Indomethacin	Soluble	ER	SE	58
27	Captopril	Soluble	ER	Coacervation	59
28	Mitomycin		ER	Coacervation	60
29	Zidovudine	Soluble	ER	SE	16
30	Zidovudine	Soluble	ER	Double emulsion solvent diffusion	17
31	Sulfisoxazole	Insoluble	ER	Coacervation	61
32	Pentazocine HCl	Soluble	ER	Coacervation	62
33	Alachlor and metolachlor	Insoluble	CR	SE	63
34	Tizanidine	Insoluble	CR	Modified SE	64
35	Becampicillin	Insoluble	ER/Taste masking	SE	65
36	Dursban	Insoluble	ER	SE	66
37	Lamivudine	Insoluble	ER	SE	67
38	Metformin HCl	Soluble	CR	Different methods	31

Table 1. cont.

No.	Drug	Water solubility	Formulation	Technique employed	Reference
39	Acyclovir	Insoluble	ER	SE	69
40	Acyclovir	Insoluble	CR	SE	70
41	Metronidazole	Soluble	SR/Stability	Coacervation	71
42	Adriamycin and Carbaplatin	Insoluble	SR	Coacervation	72
43	Verapamil	Soluble	ER	Hot melt technique	73
44	Fluconazole	Insoluble	ER	SE	74
45	Aceclofenac	Insoluble	Enteric microcapsules	SE	75
46	Salicylamide	Insoluble	CR	SE	26, 27
47	Urea	Soluble	Transdermal delivery	SE	76
48	Sumatriptan succinate	Soluble	Nasal drug delivery	Modified SE	77
49	Ondansteron HCl	Soluble	SR	SE	78
50	Prophenazine	Insoluble	ER	SE	79

DS = diclofenac sodium, TH = tramadol hydrochloride, SS = salbutamol sulfate, SE = solvent evaporation, MR = modified release, CR = controlled release, ER = extended release and SR = sustained release.

Beside these, are the following techniques most commonly employed for the preparation of EC microparticles. Coacervation-phase separation, in general, is conducted under incessant stirring and consists of three stages such as the preparation of three immiscible chemical phases, film application, and firming of the film. This technique is further classified into two subtypes such as simple coacervation and complex coacervation. Simple coacervation involves phase separation of a colloid by adding a sturdily hydrophilic material. The complex coacervation is principally a pH, temperature, solvent or salt dependant phase separation technique, which typically involves two or more than two colloids (1, 2).

Solvent evaporation technique is comparatively simple and has been applied for the encapsulation of a number of pharmaceuticals (Tables 1–6). It involves two steps such as the preparation of emulsion containing polymer and drug with a supplementary medium in which the drug and polymer cannot dissolve, followed by the complete removal of solvent. There are numerous formulation and method specific considerations that may influence the characteristics of microspheres. These factors may include the physicochemical nature of core material, type and amount of the dispersing agent, drug-polymer ratio, and the agitation speed (16, 17). Microencapsulation by rapid expansion of supercritical fluids has also been conducted mostly for the encapsulation of vitamins and pesticides. Supercritical fluids are extremely compressed gasses that own numerous characteristics of both liquids and gases. A well known example of supercritical fluid is supercritical CO_2. This technique involves many steps such as supercritical fluid containing the active ingredient and the shell material are maintained at high pressure and then released at atmospheric pressure through a small nozzle. The sudden drop in pressure results in the desolvation of the shell material, which is then deposited around the active ingredient (core) and forms a coating layer (1).

Microencapsulation by spray-drying is a cost effective process. It is commonly used for the encapsulation of flavors and oils. This process involves the dispersion of core particles in a polymer solution and its spray into a hot chamber. The polymer material solidifies onto the core particles as the solvent evaporates (2).

The techniques employed to develop microparticles or microspheres have been investigated over the last two decades, so that the concept of the wide use of microencapsulation has now become a reality (19). But in fact, none of encapsulation methodology is ideal. Many researchers have altered and/or modified several of the encapsulation techniques to achieve specific goals and for it they should adopt an in-depth approach.

Table 2. Microencapsulation of pesticides and insecticides using single polymer.

No.	Drug	Formulation	Technique employed	Reference
1	Norfluazone (Pesticide)	ER	SE	80
2	Herbicide (2,4-D)	ER and photo-degradation	SE	81
3	Herbicide (Cyanazine)	ER	SE	82
4	Rodenticide (Warfrin, ZnP, Norbromide, α-Chloralose)	MR	Coacervation	83

Abbreviations – see footnote in Table 1.

Table 3. Microencapsulation of fragrances and edibles using single polymer.

No.	Drug	Formulation	Technique employed	Reference
1	Biomaterials	To study the effect of drying conditions	Supercritical CO_2 spray drying	84
2	Propolis ethanolic extract	Taste and odor masking	SE	85
3	Moxaleaf powder	Stability/ER	Coacervation	84
4	Vitamin (Folic acid)	MR and photo -degradation	SE	86
5	Vitamin C	Stability	Different techniques	87
6	Vitamin B12	ER	SE	88
7	Polyaniline	MR and photo -degradation	SE	89
9	Rose marry oil	Durable fragrance/ Grfting onto cotton substrate	Coacervation	90
10	Lavender oil	Grfting onto cotton substrate	SE	91
11	Food additives	Stability	SE	92
12	Food additives (Fatty acids)	SR	Spray cooling	93

Abbreviations – see footnote in Table 1.

Evaluation of microcapsules

The important pre-requisite for the successful use of microencapsulation technology involves the in-depth evaluation of the characteristics of microcapsules. A collection of microcapsule characteristics has been described in some reviews. Among these characteristics, size distribution, flow properties, encapsulation efficiency, determination of loss of wall material, wall thickness, determination of density and porosity, and *in vitro* dissolution have been evaluated using following methods (14, 20).

The scanning electron microscopy (SEM) and atomic force microscopy (AFM) have elaborated the structural characteristics of microparticles as to be varying and complex. It may be discrete or aggregated as shown in Figure 1 (21). Aggregated microparticles exhibit a great variation in size and shape. The ideal discrete microparticles are acquirable by developing the microparticles as a liquid dispersed phase prior to the solidification (1). The internal and external morphology of microparticles can be explored by SEM of surfaces or sections, respectively (22). The quantitative measurement of their porosity, tortuosity and crystallinity is difficult. The efforts are being made to calculate permeability and porosity from other parameters such as release profiles and dimensions of microcapsules (23). Their size distribution has also been often studied (24). The size distribution can be determined by sieve analysis, optical microscope and laser diffractometery (24).

The assessment of flow properties is of basic importance in formulation development. The bulk density of a powder bed is not uniform (14). Thus the physical characteristics of the bed are not uniform either. Of primary importance to a formulator, when preparing microcapusles is to investigate the influence of microencapsulation method on the compactibility and compressibility of microcapsules. Therefore, the bulk density, angle of repose, Hausner's ratio, and consolidation index of the microparticles should be determined in order to standardize the product (25).

Bulk density = sample weight / sample volume

Angle of repose = $\tan^{-1} h / r$ (where r is the radius and h is the height.).

Hausnner's ratio = Volume before taping / Volume after taping

Consolidation index = Ci = {(Initial volume – Final volume) / Initial volume} × 100

The porosity of microcapsules can be calculated using the following formulas (25):

Table 4. Microencapsulation of various drugs using two polymers.

No.	Drug	Formulation and technique employed	Reference
1	DS	Inner wall-Alginate Outer wall-EC by emulsion spray drying	94
2	Nimesulide	Inner wall-Chitosan Outer wall-EC	95
3	DS	Inner wall-Gelatin and albumin Outer wall-EC by Emisification-crosslinking	96
4	5-Amino salicylic acid	Inner wall-Gelatin by SE Outer wall-EC by coacervation	97
5	Cephradine	Inner wall-EC by SE Outer wall- Chitosan by doping	98
6	Ketoprofen	Inner wall-Eudragit Outer wall-EC/EC-CMEC blend	99
7	DS	Inner wall-Chitosan Outer wall-EC	100

Abbreviations – see footnote in Table 1.

Table 5. Microencapsulation of various drugs using mixed coating / grafting / composites / co-polymers.

No.	Drug	Formulation	Technique employed	Reference
1	Allopurinol	PNIPAM-EC graft	Spray drying	101
2	Aspirin	CAP + EC blend	Emulsion SE	102
3		MC-EC blend	Super-critical antisolvent technique	103
4	Zidovudine	Sodium alginate into HPMC-EC blend	Ionotropic gelation	104
5	Nifedipine	Ammonio-Methacrylate copolymer blend	Coacervation	105
6	Theophylline	Cellulose triacetate-EC (dual and composite)	Three techniques	106

Abbreviations – see footnote in Table 1.

Table 6. Microencapsulation of various drugs using three polymers.

No.	Drug	Formulation	Technique employed	Reference
1	Clarithromycin	Chitosan-alginate-EC floating microparticles	Emulsion SE and ionic gelation	107

porosity = $1 - (W_{EC} d_{drug} + W_{drug} . D_{EC}) d_{microcapsules}/d_{drug} . d_{EC}$ where "W" and "d" stands for weight and density, respectively.

The percentage loss of wall material is calculated by following way. The total weight (W_T) of encapsulated product for a batch was calculated as (26, 27):

$W_T = W_o - F$

The weight (W_{EC}) of coat in the product is obtained from:

$W_{EC} = W_T - W_{EC}$

If W_{EC} is the initial weight of coating polymer added for microencapsulation, then:

Percentage loss of wall polymer = $100 (W_{EO}-W_{EC})/W_{EO} = 100 [1+W_O/W_{EO} (1–1/F)]$

In case where, $W_O = W_{EO}$, then:

Percentage loss of wall polymer = $100 (2–1/F)$

The wall thickness of the microcapsule is determined from the particle size of drug and the relative densities of the drug and the wall polymer. Before doing in-depth calculations, two assumptions are made, (i) drug particles are considered spherical and the microcapsule wall is uniform and (ii) microcapsule consists of two spheres. The mean spherical wall thickness is determined as (26, 28):

$r_2 - r_1 = \{[(d_C/d_{EC})(1/F - 1)]^{1/3}-1\}r_1$

where r_1 = mean radii of microcapsules, r_2 = mean radii of microcapsules, d_C = density of drug, d_{EC} = density of EC.

To determine encapsulation efficiency, a weighed quanitity of microcapsules is either powdered and suspended in a suitable solvent system such as methanol (29), methanol plus water (30), 0.1 M HCl or is dissolved in a small amount (approximately 20 mL per gram of microcapsules) of EC solvent (such as methanol, methylene chloride). The EC coat dissolves away and some amount of water is added followed by the centrifugation and then the analysis of supernatant layer. Alternatively, EC microparticles are ground into uniform white suspension in the presence of a small amount of water. The white suspension is diluted with water and sonicated for complete dissolution of drug into water. The solution is filtered to remove undissolved EC. The filterate is analyzed to determine drug contents and calculations are made to determine encapsulation efficiency by the formula (14):

Encapsulation efficiency = Weight of drug in microcapsules / Weight of drug used

As evident from *in vitro* dissolution tests, major modes of drug release from EC based microparticles (31, 32) include diffusion and erosion. Diffusion is the most commonly involved mode wherein the dissolution medium penetrates the coat, dissolves the drug and diffuse out through the interstitial channels (33). Such type of drug release kinetics obeys Higuchi's equation (33): $M_t = M_o + K_H t_{1/2}$.

In this equation, M_t indicates the cumulative amount of drug released at any specified time point and M_o represents the initial amount of drug in the formulation. The K_H is the rate constant for Higuchi model.

Erosion of polymer due to hydrolysis also causes drug release (34). Anomalous mode of drug release is generally observed from EC based microcapsules, which indicate two joint phenomena i.e., diffusion and erosion in the release of drug.

A great diversity in model drug release has been observed, which may be due to physico-chemical properties of the drug and developed microparticles like solubility of drug and drug to polymer ratio (35). It makes the development of drug release models a difficult task. However, in the light of various studies regarding the release behavior, a following generalization can be presented, i.e., EC based microparticles dissolved drug exhibit $t_{1/2}$ dependent release rate for the first half of the total drug release and thereafter decline exponentially. Such type of drug release behavior is termed a biphasic drug release.

In microcapsules, the distance traveled by drug is not constant; the drug at the center travels a longer distance than the drug embedded at the surface. Therefore, the rate of drug release generally decreases with time (36).

Materials encapsulated into the ethylcellulose microparticles

The extensive literature survey exhibits that the materials that have been encapsulated into EC microcapsules are solids, liquid and gases. The composition of the encapsulated materials (37–107) can be varied, as the liquid core can contain dispersed and/or dissolved materials, whereas the solid core may consist of active pharmaceutical ingredient, stabilizers, and release-rate retardants or accelerators (Tables 1–6).

EC microcapsules have been prepared by single coating of EC around various chemical substances like different drugs, pesticides, insecticides, fragrances and food edibles (Tables 1–3).

EC microcapsules have also been prepared by double coating of two different polymers having EC as one of the two coating materials (Tab. 4). Kang and Kim (94) prepared ethylcellulose microparticles possessing alginate and calcium carbonate microparticles by spray drying water-in-oil emulsion. Alginate solution (3%) in distilled water was

employed as an aqueous phase, ethylcellulose solution (5%) in dichloromethane as an oil phase, and sorbitan sesquioleate as an emulsifying agent. The microparticles of calcium carbonate were dispersed into the emulsion. Ultimately, ethylcellulose microparticles containing alginate and calcium carbonate were obtained by spray-drying the emulsion. Khan et al. (95) formulated ethyl cellulose (EC) microparticles for sustained release of nimesulide by coacervation (temperature change) technique and study the influence of various variables, drug to polymer ratio and also observe the drug polymer compatibility. Saravanan et al. (96) prepared diclofenac sodium loaded gelatin and albumin magnetic microspheres by emulsification/cross-linking by glutaraldehyde using ethylcellulose in chloroform and sesame oil with/without span80 as stabilizer. Atyabi et al. (97) prepared and evaluated a double coated multiparticulate system for 5-ASA delivery using gelatin and ethylcellulose as the primary and secondary polymer, respectively, to prepare a delayed drug delivery system, in which ethylcellulose protects particles for the first 6 h transit through the gastrointestinal tract. Gelatin microcapsules containing 5-aminosalicylic acid were developed using the solvent evaporation technique. Gelatin microspheres were then coated by ethylcellulose using a coacervation phase separation method. Takishima (98) prepared cephradine-containing ethylcellulose microparticles (MPC) by the solvent evaporation method, while chitosan-coated MPC (Chi-MPC) were developed by doping MPC with viscous chitosan solution and subsequently drying. Yamada et al. (99) prepared microparticulate systems for sustained release of ketoprofen in the form of calcium salt (KP-Ca) and evaluated by monitoring drug release in the JP XIII second fluid, pH 6.8. To develop polymer-coated microparticles of ketoprofen, eudragit microparticles of KP-Ca (ER-MP) were first developed, and then coated with ethylcellulose or with a mixture of carboxymethylethylcellulose (CMEC) and ethylcellulose to formulate ethylcellulose-coated (EC-coat) and the mixture-coated microparticles (CMEC/EC-coat), respectively. Remunan-López et al. (100) proposed a new microparticulate chitosan (CS) controlled release system that consisted of hydrophilic CS microcores entrapped in a hydrophobic cellulose acetate butyrate (CAB) or ethyl cellulose (EC). These microcapsules were acquired with different types of CS and various core/coat ratios.

EC microcapsules have also been prepared by tripple coating of two different polymers having EC as one of the three coating materials (Tab. 5). Zhang et al. (107) described the development of a gastric floating-bioadhesive drug delivery system to enhance the efficacy of clarithromycin against *Helicobacter pylori*. Floating-bioadhesive microparticles containing clarithromycin were developed by a combined method of emulsification/evaporation and internal/ion gelation for the management of *H. pylori* infection. Ethylcellulose microcapsules (EMs) were prepared by the dispersing clarithromycin, ethylcellulose, and chitosan in dichloromethane and subsequent solvent evaporation. EMs were coated with alginate by the internal gelation method to get alginate-ethylcellulose microparticles (AEMs); then, AEMs were dispersed in a chitosan solution, and chitosan-alginate-ethylcellulose microparticles (CAEMs) were acquired by ion gelation to increase the bioadhesive characteristics.

EC microcapsules have also been prepared by grafting/mixed caoting of two or more more different polymers having EC as one of the two coating materials (Tab. 6). Kim et al. (101) synthesized the thermo-sensitive polymer, PNIPAM-grafted ethylcellulose. It was confirmed by FTIR spectroscopy that PNIPAM was successfully grafted onto ethylcellulose. Microparticles were developed by the spray-drying method using a B-191 Mini Spray Dryer. Dash et al. (102) conducted the microencapsulation of aspirin and then studied its release kinetics. The encapsulation was conducted by emulsion solvent evaporation method using ethylcellulose (EC), cellulose acetate phthalate (CAP) and their mixture (1:1) of polymeric constituents. Duarte et al. (103) used the supercritical antisolvent (SAS) technique to prepare ethyl cellulose/methyl cellulose blends, two biocompatible polymers commonly used as drug carriers in controlled delivery systems. Agrawala et al. (104) encapsulated drugs in the polymers of varying solubility in an aqueous environment. The microcapsules were developed using ionotropic gelation technique, where gelation of anionic sodium alginate, the primary polymer, was produced with oppositely charged counter ion to develop microparticles which were further made sustained by using different polymer, namely: hydroxypropyl methylcellulose, ethylcellulose and mixture of both these polymers. Zidovudine, an antiretroviral drug, was selected as novel drug for this study. Huang et al. (105) developed and evaluated nifedipine-loaded microcapsules to elucidate the controlled-release mechanism of nifedipine from microcapsules of ammonio methacrylate copolymer and ethylcellulose binary blend prepared by a phase-separation method. Wu et al. (106) investigated three microencapsulation techniques using cellulose

triacetate as an added complementary coating material in the development of sustained-release ethylcellulose-cellulose triacetate microcapsules of theophylline. Ethylcellulose-cellulose triacetate composite microcapsules, ethylcellulose-cellulose triacetate dual-walled microcapsules and ethylcellulose microcapsules containing cellulose triacetate matrices were developed using the non-solvent addition phase separation method.

CONCLUSION

EC based microencapsulated system is developed as unique carrier system for many pharmaceuticals and can be tailored to release drug slowly. The molecular weight (viscosity) grade of EC can influence the drug release rates. Drug release is decreased with increasing molecular weight (viscosity) of EC. The decrease in drug release can be attributed to an improvement in the mechanical properties of EC film. Alternately, the use of plasticizer (pore formers) in the encapsulating system can slow down the drug release, since the plasticizer reduces the internal stress of coating, making the film more sounder and coherent. Higher molecular weight (viscosity) EC grade provides film of higher mechanical properties. Further studies can be designed to explore the influence of various plasticizers into EC coating to achieve ideal controlled drug release and to develop modeling for EC based formulations using model pharmaceuticals with different physico-chemical properties. Although significant advances have been made in the field of microencapsulation, there are still many challenges ahead in this field.

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