

Formulation of Extended Release Multiparticulate Systems using Ethylcellulose

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Multiparticulate systems for oral extended release have been successfully developed and marketed due to their unique manufacturer and patient benefits that are realized. The formulation advantages are release profile modulation and combination therapy, and clinical benefits are ease of swallowing (paediatric and geriatric focus), consistent release profiles and minimal risk of dose dumping. This article will review the critical formulation aspects of multiparticulate core manufacturing considerations with emphasis on barrier membrane coating using ethylcellulose for oral extended release applications.

Introduction:

Oral administration is preferred route of drug administration for most therapeutic agents [Banker et al, 1986]. In addition, much effort has been directed in developing modified release oral dosage forms allowing for better control of drug therapy [Rane et al, 2010].

Multiparticulate (MP) systems have been successfully used for oral controlled drug release. These are small, spherical or irregular shaped particulates systems, which contains the drug with a release retardant method, such as a barrier membrane coating. MP systems have attracted much attention due to the many advantages associated with them;

1. High degree of flexibility in the design and development of dosage forms.
2. They can be divided into the desired dose strengths without formulation or process changes.
3. Different MP systems may be blended to deliver incompatible bioactive agents in a single dosage form, or to provide different release profiles.
4. MP systems disperse freely in the GI tract, maximize drug absorption.
5. Variations in gastric emptying rates and overall transit time are reduced for MP and hence may reduce inter- and intra patient variability.
6. Provide a suitable option for paediatric/geriatric formulations due to their swallow-ability, when mixed with food.

Each subunit in an MP system, contain part of the drug and the sum of the drug in all subunits make the total dose, but the functionality of the overall dose is directly correlated to the functionality of individual

subunits. The chances of all subunits accidentally release their drug content is low and thus the risk of dose dumping using MP system is generally lower compared to single unit systems [CPMP/QWP/604/96].

There has been extensive research on refining and optimizing pelletization techniques which have given the pharmaceutical scientist the opportunity to apply scientific principles to the development of well-designed and predictable controlled-release MP dosage forms. On the basis of manufacturing methods, the drug containing seeds for the development of extended release MP systems have been divided in following types:

1. Drug layered pellets
2. Extruded and spheronized pellets
3. Mini-tabs

This article provides an overview of the important considerations of MP manufacturing along with barrier membrane coating using ethylcellulose for extended release applications.

Manufacturing considerations of MP for extended release formulations

Typical manufacturing method for MP consists of the following steps:

Substrate containing drug → Seed (if required) → Barrier membrane → Top coat (reduce electrostatic and protect functional membrane)

1. Core considerations

1.1 Drug layering on starter seeds

Starter seeds are inert carrier material such as sugar spheres (e. g. SureSpheres®), micro crystalline cellulose spheres, silica beads, or others that are

used for drug layering. Sugar spheres are widely used in formulations due to their acceptability and availability in various size ranges. The important aspect during drug layering is to achieve a uniform drug layer to ensure content uniformity.

It is desirable to have smooth starter cores in order to achieve reproducible drug release profiles. **Figure 1** shows a comparison of drug release using starter seeds with smooth versus rough surfaces, drug layered and barrier membrane coated. The release from a smooth core was found to be slower than the rough core. This has been attributed to a uniform drug layer and barrier membrane coat on the smooth core as compared to the rough surface core. The roughness may have created weak points in the coating that lead to increased drug release rates.

It is important that the starter seeds have a narrow and consistent particle size distribution. Changes to the size distribution may influence surface area available for drug layering and coating and thus affect drug release rate. A decrease in particle size from 14-18 mesh (1000-1410 µm) to 30-35 mesh (500-590 µm), significantly increased the release rate of chlorpheniramine maleate when similar weight gains of barrier membrane coat was applied (**Figure 2**) [Rege et al, 2005]. This has been attributed to a decreased film thickness of the barrier membrane coat arising due to increased surface area with the smaller sized pellets.

A narrow particle size distribution will ensure a minimum variation in the coating thickness throughout the different batches of pellets thus resulting in uniform performance for pellets from batch to batch. This could also help in reduced segregation during capsule filling or tablet compression of the coated pellets.

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Tolerances on the particle size distribution of the substrate must be established to maintain the consistency of the coated product. It is important to have a well qualified vendor in place for sourcing starter cores that ensures lot- to-lot uniformity in the quality of the starter cores. Another important quality of the starter core is their hardness. It is equally important that the starter cores are tough enough to withstand the rigors of the Wurster coating process. Friable starter cores may break down during processing, leading to process loss and may also result in a changed surface area.

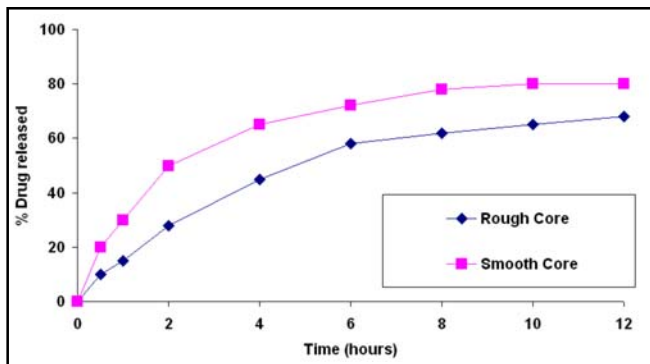


Figure 1: Effect of substrate surface properties on drug release

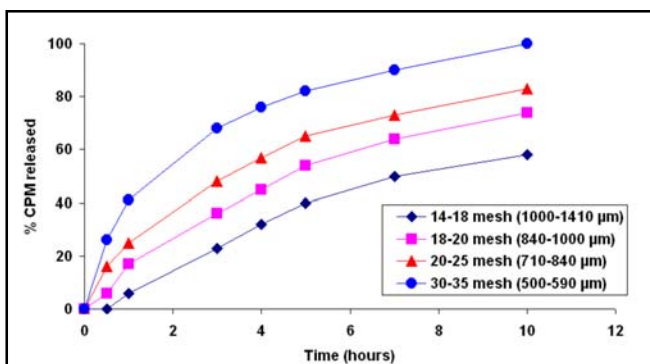


Figure 2: Effect of pellet size distribution on drug release

Drug can be applied to starter seeds by:

1. Powder layering
2. Solution/suspension layering

1.1.1 Powder layering

Powder layering is considered to be the oldest method for coating drug particles on a substrate. During powder layering, a binding solution and a finely milled powder are added simultaneously on the bed of starter seeds at a controlled rate in a pan or suitable equipment. The process is continued until the required sized pellets or target potency is achieved. It is extremely important to deliver the powder accurately at a predetermined rate throughout the process and in a manner that maintains equilibrium between the binder liquid addition rate and the powder addition rate. If the powder addition rate is high, dust generation may occur, and if the liquid addition rate is high, over wetting of the pellets may take place. Powder layering can be carried out in a pan or a tangential spray or centrifugal fluid bed granulator.

In conventional coating pan, tilt angle and rotational speed must be optimized for powder layering. If the pan speed is too slow, segregation may occur owing to percolation and induce the preferential layering of drug onto larger particles. Newer equipment like tangential spray or centrifugal fluid bed granulators have also been used for powder layering process.

Binders are required during powder layering process to provide

good binding for drug particles on the starter core. For this, binder solutions must have high binding capacity. Micronization of the drug, before layering improves the efficiency of the process significantly and provides morphologically smooth pellets that are suitable for further coating. Micronization may, tend to reduce the powder flow and therefore addition of a glidant is recommended. Finally, the coating parameters like bed temperature and air flow must be optimized based on equipment used to develop a robust formulation.

1.1.2 Solution/suspension layering

The drug may be applied to the starter seeds in solution or suspension form. Selection of the layering process depends on solubility and/or stability of the drug. It is possible to use water or organic solvent or hydroalcoholic medium for layering process. Presently, most of the pharmaceutical industry prefers to use aqueous systems when ever possible. There are several advantages in aqueous processing, such as environmental considerations with no health hazards to workers, no need for special solvent recovery systems, no issues of organic volatile impurity and also offers economic advantages over organic process.

During processing, all the components are first dissolved or suspended in an appropriate quantity of the medium which is then sprayed onto the starter seeds bed. The sprayed droplets immediately impinge on the starter seeds and spread evenly on the surface, provided the drying conditions and fluid dynamics are favorable. This is followed by a drying phase that causes the dissolved material to precipitate and form solid bridges that would hold the formulation components together. Successive layers are formed on the starter cores as process continues until the desired quantity of drug substance is sprayed on the starter core.

For suspension layering, particle size of the drug plays an important role. If the particle size is large, a higher quantity of binder may be necessary to ensure adherence of the drug particles on the pellet surfaces. Use of high viscosity binders and stirring of the suspensions during applications, are recommended in order to avoid any settling of the drug particles. Use of very large particle may block the spraying gun or may settle in the tubing if the diameter of the tube is too large. For suspension layering process, the particle size of the API should be less than 10 - 50 µm.

In solution layering, it is likely that solution may not require any binder and may bind to the substrate alone. Recrystallization can produce a layer that may appear to be naturally smooth and free from defects. The drug layer, however, may be brittle and may delaminate or break off from the core. Inclusion of a binder helps to alleviate this problem.

The viscosity of the spraying solution should be preferably in the range of 200 - 300 cPs for ease of pumping and atomization. The API may contribute to the viscosity of the solution. High dose API's may result in drug solutions with increased tackiness, limiting the spray rate and increasing the total process time. Dilution and/or decreasing the spray rate or addition of talc to the solution may help in reducing the tackiness. For very low dose drug, dilution of the system is required to ensure content uniformity of the API. Binders are generally used during solution/suspension layering to impart strength to the pellets. Commonly used binders are; low viscosity hydroxypropoxymethylcellulose or formulated systems like Opadry®. Other ingredients that may be used during drug layering process are stabilizer, surfactants, or pigments.

A bottom spray, fluid bed coater is commonly used equipment for solution / suspension drug layering.

1.1.3 Seal coat

Sometimes a seal coat may be applied to the starter core or drug containing pellets to: (1) Improve the hardness of the friable starter seeds or drug layered pellets, (2) Separate the drug from

the core or the barrier membrane, if incompatible (3) Provide a smooth surface on drug loaded pellets for further functional coat, (4) Reduce or control the influence of osmotic pressure exerted by sugar (starter seeds) on drug release. For seal coating, low viscosity METHOCL™ (hydroxypropylmethylcellulose), ETHOCEL™ (ethylcellulose), or formulated systems like Opadry® (complete film coating system) or Surelease® (aqueous ethylcellulose dispersion) are recommended.

1.2. Extrusion and spheronization

Extrusion process involves a preliminary stage in which dry powders of drug and excipients are mixed in conventional blenders, followed by addition of a liquid to develop wet mass. The wet mass is extruded through cylindrical dies or perforated screens with circular holes, typical 0.5 - 2.0 mm in diameter to form cylindrical extrudates. These may be further processed, by cutting and drying to yield cylindrical granules. The extruded strands are transferred into a spheronizer, where they are instantaneously broken into short cylindrical rods on contact with the rotating friction plate and the process is repeated until pellets of the desired sphericity are obtained. These spheroids can be used as such for drug delivery or usually coated with a polymer to control the rate of drug release after drying [Erkoboni, 2003]. The technology is normally used for the manufacture of pellets with a high drug loading. The technology may be used to produce extended release pellets in a single step

using a carrier polymer similar to the matrix concept.

The quality of pellets is highly influenced by the process parameters associated with the extrusion stage and is widely studied by various research scientists. Pellets properties such as morphology, size distribution, porosity and sphericity along with other formulation parameters such as presence and absence of soluble or insoluble fillers, surface active agents, pH modifiers, drug load, drug filler ratio influence the drug release profile [Breitenbach, 2002].

1.3. Mini-tabs

Mini-tabs are small tablets with a diameter of about 2-5 mm that may be filled into hard capsule shells [Lennatz *et al*, 1998]. Mini-tabs combine the advantages of MP dosage forms with the established manufacturing techniques of tableting and include fewer constraints than for example extrusion and spheronization process [Riss *et al*, 2007].

Mini-tabs follow the same manufacturing process as conventional tablets and use similar formulation and process considerations. Mini-tabs may be produced using conventional tableting machines with minor modifications. For example, in order to increase production speeds, multiple-tip tooling may be used.

Drug release may be modulated at the core level by using different release retardant polymers and further modified by

coating the mini-tabs similar to multi-particulates. Mini-tabs are coated in fluid-bed process and in modified coating pans (to handle small sizes of the mini-tabs).

2. Barrier membrane coating

Dosage forms where an applied film controls the rate of drug release are called as 'barrier membrane controlled' systems. In barrier membrane controlled system, a polymer layer of retardant material is placed between the drug and the dissolution medium. In such a system, the drug diffuses out through the rate controlling membrane, into the surrounding medium. The film forming polymer often requires the addition of other excipients such as plasticizers, pore formers, or anti-aggregation agents for the product to be conveniently manufactured or for the coating to perform in the desired fashion [Rhodes and Porter, 1999].

Several drug release mechanisms have been proposed from MP dosage forms coated with water insoluble polymers (a) solution & drug diffusion through the continuous polymer phase, (b) solution & drug diffusion through channels produced by plasticizer or pore-formers (c) osmotically assisted drug release [Ozturk *et al*, 1990].

Drug release across the membrane where a water insoluble membrane encloses a core reservoir is described by Fick's 1st law of diffusion (**equation 1**) [Aulton, 2001]

Table; 1 Characteristics of different multiparticulates.

	Drug-layered	Extruded spheronized	Mini-tabs
Dose / Drug	Lower doses (<50 mg)	Higher doses (>50 mg)	High or low doses
Geometry	Isometric spheroids		Cylindrical/ convex
Manufacturing process	Slow	Multistage, complex	Conceptually simple
Potential Variables	<ul style="list-style-type: none"> - Starter core quality - Equipment type - Binder type & level - Solution Vs. Suspension - Solid content - Aqueous or organic - Process parameters 	<ul style="list-style-type: none"> - Blending - Granulation - Equipment type - Spheronization - Process parameters - Particle size - Pellets properties - Moisture content 	Similar to tablet manufacturing
Processing steps	<ul style="list-style-type: none"> - Placebo seeds - Drug Layering - Seal Coating - Functional coatings 	<ul style="list-style-type: none"> - Blending - Granulation (HS, LS, FB, RC, RG) - Extrusion - Spheronization - Drying - Sieving - Seal Coating - Functional coatings 	<ul style="list-style-type: none"> - Blending - DC/ Granulation - Sieving - Drying - Compression - Seal Coating - Functional coatings
(b) Secondary	Encapsulation or compressed to tablets		

HS - High shear, LS - Low shear, FB - Fluid bed, RC - Roller compaction, RG - Rotor granulation, DC - Direct compression.

$$[dM] / [dT] = [ADK \Delta C] / [l] \text{ ----- (eqn. 1)}$$

where A - Surface area, ΔC - concentration gradient, D - diffusion coefficient, K - Partition coefficient, and l - diffusion path length.

For any given drug and formulated system; A, D, K & ΔC would remain nearly constant. Therefore, the rate of drug release is inversely proportional to diffusion path length. Here, the diffusion path length is the thickness of the barrier membrane coat. So, increasing the film thickness (or weight gain) would reduce the drug release rate by increasing diffusion path length. For barrier membrane film, changing the permeability at constant weight gain would also help to modulate the drug release profile. Different types of drug release profiles are achieved on the same pellets by changing the thickness or the permeability of the barrier film coat.

Commonly used polymers in barrier controlled systems are cellulose derivatives, acrylic polymers and polyvinyl acetate. Amongst these, the cellulose derivative, ethylcellulose, is extensively used in barrier membrane controlled release application [Porter, 1989] which is reviewed here.

2.1 Ethylcellulose

Ethylcellulose (EC) is partly O-ethylated cellulose. It contains not less than 44.0 percent and not more than 51.0 percent of ethoxy (-OC₂H₅) (Figure 3). Table 2 describes various grades of ETHOCEL™ available from CR Alliance (Dow chemical company and Colorcon).

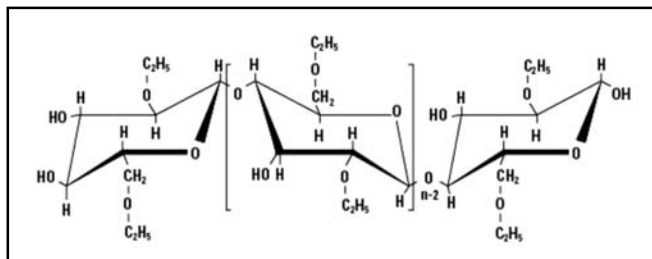


Figure 3: Chemical structure of ethylcellulose

Table 2: ETHOCEL™ range of polymers (Dow Chemical Company product brochure)

Product Viscosity Designation	Solution Viscosity* range (cP)	Ethoxyl Content (%)
ETHOCEL™ Standard 4 Premium ethylcellulose	3 – 5.5	48.0 – 49.5
ETHOCEL™ Standard 7 Premium ethylcellulose	6 – 8	48.0 – 49.5
ETHOCEL™ Standard 10 Premium ethylcellulose	9 – 11	48.0 – 49.5
ETHOCEL™ Standard 20 Premium ethylcellulose	18 – 22	48.0 – 49.5
ETHOCEL™ Standard 45 Premium ethylcellulose	41 – 49	48.0 – 49.5
ETHOCEL™ Standard 100 Premium ethylcellulose	90 – 110	48.0 – 49.5

* Note: Viscosities are for 5% solutions measured at 25 Degree C in an Ubbelohde viscometer. The solvent is 80% toluene and 20% ethanol.

2.1.1 Organic application of ethylcellulose (EC)

Ethylcellulose (EC) is insoluble in water and soluble in various organic solvents which make it ideal options for organic coating. EC is soluble in alcohols, chlorinated hydrocarbons, esters, ethers, aromatic hydrocarbons and ketones, and most soluble in blends of

aromatic hydrocarbons and aliphatic alcohol. Some solvents are excellent in dissolving the EC polymer, but have limited or no applications in the pharmaceutical industry since they are not approved for pharmaceutical use.

The following sequences of events have been reported to occur during EC coating from an organic solution [Onions, 1986]:

- During spraying, the initial evaporation of the solvent leads to an increased polymer concentration in the droplet and increased viscosity.
- Long polymer chains start overlaying on one another until, a dry gel structure forms in the final stages of drying.
- The polymer solutions then undergo sol to gel transitions upon solvent evaporation to form the polymeric film.

All these events occur rapidly during film coating applications and not visible, however, microscopic examination of the EC film have been shown to appear as stacked in a 'straw pile' indicating long overlaying polymer chains [Dias *et al*, 2009].

2.1.2 Influence of ETHOCEL™ polymer viscosity grade on drug release

Films prepared from low viscosity grade polymers with short chains are relatively weak and as the chain length increases, the mechanical properties of the films improve until at some critical molecular weight there is no further improvement. These improved mechanical properties of the film may contribute to slower drug release as the polymer molecular weight increases [Rowe, 1992]. Dias *et al* [2009b] studied the effect of ETHOCEL™ viscosity grades on drug release from barrier membrane coated chlorpheniramine maleate pellets. Figure 4 shows that as the viscosity grade of ETHOCEL™ increased there was a gradual retardation of drug release, and increased lag-time. However, beyond a certain critical viscosity grade of ethylcellulose, there was no further decrease in drug release rate.

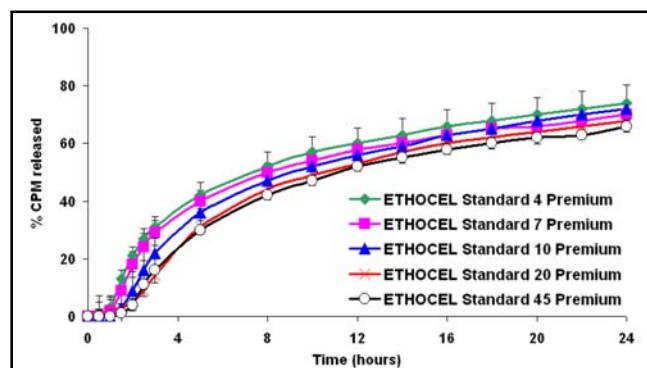


Figure 4: Effect of ETHOCEL™ viscosity grade on chlorpheniramine maleate release profiles from ETHOCEL™ coated pellets at same coating weight gain

As the viscosity grades of EC increases, it necessitates preparing solutions with low solid content and therefore, selection of the viscosity grade of EC influences processing ease and productivity.

2.1.3 The influence of solvent system for ethylcellulose coating applications

The solvent system (vehicle) provides a medium for transporting the coating materials to the surface of the substrate. A good solvent system should provide low solution viscosity, for ease of application, and allows polymer to fully solvate and relax, yielding films with good mechanical strength for reproducibly control drug release.

Commonly used organic solvents for ethylcellulose are

dichloromethane, acetone, isopropyl alcohol (IPA) and ethanol alone or in various combinations. It is also possible to use hydro-alcoholic systems for EC coating and commonly used combinations are IPA : water or ethanol : water at 90 : 10 ratios. It is reported that solvent composition had an influence on solution viscosity of ethylcellulose, which may further affect coating process efficiency [Rowe, 1986].

It has been reported that EC films from solvent-mixtures comprising water may be porous, and result in faster drug release rates [Iyer *et al*, 1990]. However, another study reported no significant change in drug release profile with different solvent compositions at 20% coating weight gain (Figure 5) [Dias *et al*, 2008].

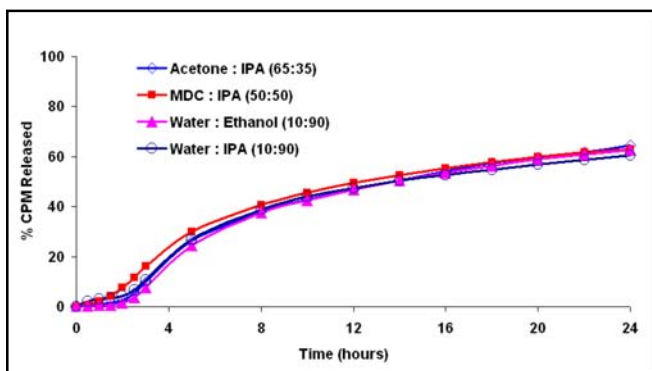


Figure 5: Effect of solvent system on chlorpheniramine maleate release profiles from ETHOCEL™ coated pellets at 20% weight gain

2.1.4 Choice and level of plasticizers suitable for ETHOCEL™ barrier membrane

Plasticizers are added to ETHOCEL™ solutions to render it more pliable and provide film with enhanced mechanical properties. In case of films prepared from low molecular weight grades of EC, where drug release is largely through flaws and cracks in the coating, the plasticizer (diethyl phthalate) was found to be advantageous in slowing the drug release. This was explained by the partitioning of the plasticizer into the EC lowering its glass transition temperature, reducing its residual internal stress within the coating, and thereby producing a more coherent film [Rowe, 1986].

Ethylcellulose is compatible with a large number of plasticizers [Dahl, 2000]. Type and quantity of plasticizers may influence the rate of drug release by altering the water permeability of the barrier membrane. Figure 6a show the influence of different types of plasticizer on drug release. Slowest drug release was observed from films plasticized by lipophilic plasticizers. A correlation between the mechanical properties of the resulting films and plasticizer molecular structure has been observed. The long chained plasticizers e. g. dibutylsebacate (DBS) are thought to penetrate the polymer chains better than the more spherical plasticizers e. g. triethylcitrate (TEC) or triacetin molecules coupled with their lipophilic nature have resulted to a slower drug release [Dias *et al*, 2009a].

Figure 6b shows that drug release decreased with increasing plasticizer content. This may be attributed to a more coherent EC film produced as a result of reduced residual internal stress within the coating. Drug release was significantly reduced where lipophilic plasticizers such as DBS, fractionated coconut oil (FCO) or oleic acid (OA) were used at 30% w/w (Figure 6b). This may be attributed to the reduced wettability and permeability to water and thus reduced diffusivity of the barrier membrane film [Dias *et al*, 2009a].

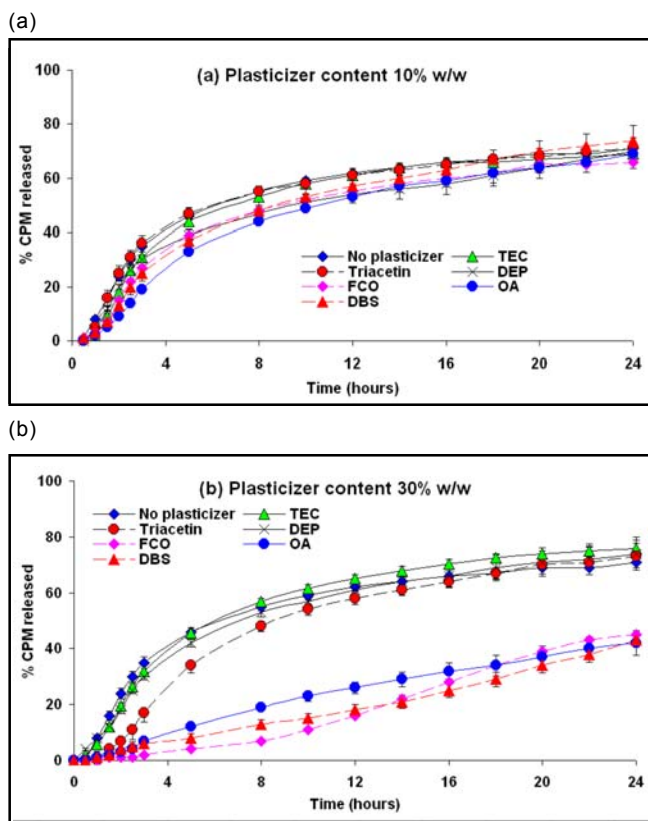


Figure 6: Influence of plasticizer choice and level on chlorpheniramine maleate release profiles from ETHOCEL™ coated pellets (a) plasticizer content 10% w/w (b) plasticizer content 30% w/w

2.1.5 Effect of pore former on drug release from ETHOCEL™ coated pellets

Pure ETHOCEL™ films may have low permeability for some drugs and require addition of permeability enhancer to modulate drug release profile. Permeability enhancers (commonly known as pore-formers) addition to a barrier membrane system may offer following advantages:

- Increase the rate of release for poorly soluble drugs.
- Leads to complete terminal phase.
- Low weight gains of a barrier membrane may be difficult to reproduce consistently at production scale, and may lead to batch-to-batch variation in release. Incorporating, pore former may allow increasing the weight gain, thereby maintaining the release profile but achieving a more robust formulation.
- May eradicate an undesirable initial lag phase in the release profile.
- May help in increasing drug release rate.

Although various pore-formers (channelizing agents) have been evaluated for EC films such as polyethylene glycol (PEG), polysorbate 20 [Munday and Fassihi, 1988], sodium chloride, sucrose [Lindholm and Juslin, 1982], use of non-ionic polymers such as HPMC [Ong *et al*, 2006] or HPC, or ionic polymers such as Na alginates, Na CMC or formulated systems like Opadry® are recommended [Levina *et al*, 2007].

Figure 7 shows that increased pore former (METHOCEL™ E6 LV) levels in EC film lead to an increase in drug release rate [Colorcon unpublished data]. Use of ionic polymer as pore formers, where the solubility of the polymer is pH dependent, unique drug release profiles such as delayed release may be achieved [Young *et al*, 2006]. Table summarizes key formulation variables affecting drug release from EC coated multiparticulate system.

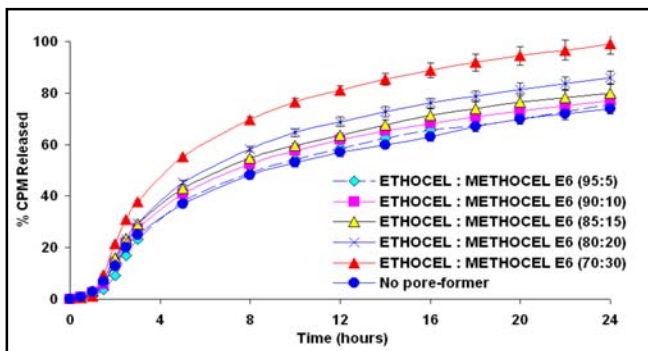


Figure 7: Effect of pore former concentration (METHOCEL™ E6LV) on chlorpheniramine maleate release profiles from ETHOCEL™ Coated pellets at constant weight gain of 10% w/w

Table 4 : Summary of key variables affecting drug release from ethylcellulose coated multiparticulate systems

Key Variable	Effect on drug release
Film thickness	● As film thickness ↑, drug release ↓
Viscosity	● As viscosity ↑, drug release ↓
Drug solubility	● As the solubility ↑, drug release ↑
Plasticizer	● Drug release is faster if water soluble plasticizer is used ● Change in plasticizer level may change the drug release
Pore former	● As pore former ↑, drug release ↑
Solvent	● Faster release from aqueous than organic coated at equivalent thickness

Conclusion:

Multiparticulate systems for oral extended release formulations systems offer distinctive benefits to formulators and clinicians. Core manufacturing and barrier membrane coating considerations are critical to the success of extended release formulation. Choice and level of molecular weight grade (viscosity grade), plasticizer, solvent for coating and pore former influence drug release profiles from ethylcellulose coated multiparticulate systems. By selecting right combination of all these parameters can offer drug release profile flexibility and robustness of the overall formulation.

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