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CONTROLLED-RELEASE FILM COATINGS BASED ON ETHYLCELLULOSE

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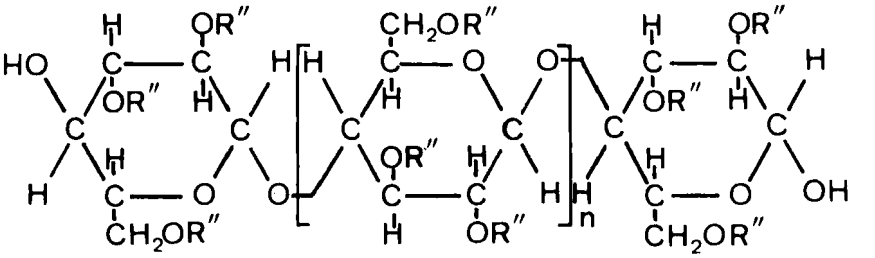
ABSTRACT

Ethylcellulose has become a polymer widely used in pharmaceutical film coating, especially when it is necessary to produce a modified-release dosage form. While initial emphasis was placed on using organic-solvent-based solutions of this polymer, more recent introduction of aqueous latex dispersions of ethylcellulose has attracted a lot of interest. This review will describe the characteristics of ethylcellulose film-coating systems, and discuss those factors (including those relating to the substrate, coating formulation and coating process) that can influence the behavior of such systems.

INTRODUCTION

What is Ethylcellulose?

Ethylcellulose is the ethyl ether of cellulose and can contain between 44.0 and 51.0 percent of ethoxy



where $R'' = C_2H_5$

FIGURE 1
Structure of Ethylcellulose

($-OC_2H_5$) groups (USNF XVI). Ethylcellulose is prepared by reacting ethyl chloride with alkali cellulose (obtained by treating crude cellulose with an alkaline solution).

The structures of ethylcellulose and that of the parent cellulose are shown in Fig. 1, where it can be seen that each anhydroglucose unit (of cellulose) has three reactive hydroxyl groups that can be ethoxylated. The structure as shown for ethylcellulose has all three hydroxyl groups ethoxylated, and consequently is said to have a degree of substitution (D.S.) of 3.0. In practice, the D.S. may vary, depending on end use of the polymer.

Typically, ethylcellulose used in pharmaceutical film coating has an ethoxyl content of 48.0 to 49.5

percent, and a D.S. of 2.41 to 2.51. This specification conforms to the Ethocel standard premium product supplied by Dow Chemical and Ethylcellulose N series supplied by Hercules.

As with most film-coating polymers, ethylcellulose is available as various grades of differing molecular weights, each grade being represented by a viscosity number as determined by measuring (ASTM D914) the viscosity of a 5% solution of the polymer in an 80:20 toluene/ethanol solvent mixture.

Suitability of Ethylcellulose for Sustained-Release Film Coating

Ethylcellulose is probably the most widely-used water-insoluble polymer in film coating and has good film-forming properties that enable tough, flexible coatings to be produced.

Ethylcellulose has many characteristics that allow the formulator a lot of flexibility in optimizing formulations, including:

- availability in a wide range of viscosity (or molecular weight) grades
- solubility in a variety of organic solvents (and organic-solvent mixtures)
- miscibility with various water-soluble materials that permit the permeability

characteristics of resultant films to be readily changed[1]

Ethylcellulose can also be readily formulated into aqueous polymeric dispersions that facilitate the use of aqueous film-coating technology.

FORMATION OF FILMS WITH ETHYLCELLLOSE

Film structure is a key factor in determining the performance of any polymeric coating. Consequently, understanding the process of film formation with any polymer coating system can help provide insight into how the final coating will behave.

Since ethylcellulose can be applied either as a solution (in organic solvents) or an aqueous "latex", there are two fundamentally different mechanisms for film formation that we need to be aware of.

Film Formation From Solution in Organic Solvents

Generally, formation of coatings from polymer solutions involves conversion of a viscous liquid into a visco-elastic solid. Simply, this process involves:

1. Rapid evaporation of solvent (typically from the surface of droplets created by a spray-atomization

technique), causing an increase in polymer concentration in the solution and contraction in volume of the coating liquid.

2. Further loss of solvent after the solvent has diffused to the surface of the coating. Concentration of the polymer in the coating increases to the point where the polymer molecules ultimately become immobilized (the so-called solidification point).

3. Additional loss of solvent (beyond the solidification point) resulting from the slow diffusion of residual solvent through the "dry" coating. Such solvent loss is very much time-dependent, and ultimately causes shrinkage stresses to develop within the coating.

From a structural standpoint, the quality of the final dried coating is very much determined by the initial interaction between the polymer and the solvent, and the volatility of the solvent system used.

Maximum interaction between the polymer and solvent (often determined by cohesive energy densities, or solubility parameters)[2], typically results in maximum chain extension of the polymer such that interaction between the polymer chains in the resul-

tant dried coating will also be high, (yielding a film with good mechanical properties).

Volatility of the solvent will play a large part in determining the tendency of the polymer solution to partially "spray dry" during application, resulting in the formation of a very porous coating.

Film Formation from Aqueous Polymeric Dispersions

Film formation from aqueous polymeric dispersions (or latices) is complex. In the liquid state, the polymer is present as discrete particles in aqueous suspension. To form a continuous film, these polymeric particles must come closely together, deform and ultimately fuse together. At the same time, the vehicle (water) must be removed.

The complexity of the film-forming process with latex systems has given rise to several competing theories.[3] Generally, however, during film formation, sufficient pressure must be set up to cause the polymeric particles to deform and coalesce. This coalescence is facilitated by capillary forces (between particles) that are generated as water evaporates. Complete coalescence can, however, only occur as the result of viscous flow which eliminates the boundaries between adjacent polymer particles. Thus "diffusion"

of polymer chains across the boundaries must occur, a process which can be to some extent accounted for by free volume theory which presumes that sufficient free volume (or intermolecular space) exists in the bulk polymer to accommodate the "diffusion" process.

The coalescence process can be dramatically affected by the **Glass Transition Temperature**, T_g, of the polymer. If the glass transition temperature of the polymer is substantially above the typical temperature conditions generated in the coating process (in this case, product or bed temperature are the important criteria), then free volume will be too low[4] and insufficient viscous flow will occur[3], to permit complete coalescence of the latex particles. Since the T_g for ethylcellulose has been reported at 135°C, then it is important that aqueous polymeric dispersions of this polymer be effectively plasticized to assure that complete coalescence of the latex particles will occur under acceptable film-coating process conditions.

FACTORS AFFECTING RELEASE OF DRUGS FROM DOSAGE FORMS COATED WITH ETHYLCELLULOSE

Dosage forms where an applied film coating provides the main means for rate control for drug release are commonly termed "membrane-moderated,

controlled-release systems" or "reservoir systems". With such a system, the active material diffuses from the core material, through the rate-controlling membrane, into the surrounding environment. Typically, such factors as membrane porosity, tortuosity, geometry, and thickness play an important part in determining the rate at which the drug can pass through the coating. A discussion of these factors (and appropriate mathematical treatment) has been given by Tojo, et al[6].

While the expected behavior of reservoir systems can be depicted by relatively simple mathematical treatment, such treatment often ignores the impact of structural irregularities in the membrane that can be related to the substrate on which the coating is applied, formulation of the coating itself, and the impact of critical processing factors.

Various additional factors that influence release of drug from a reservoir system have been discussed[7,8,9], and include:

- transport of drug through a network of capillaries (filled with dissolution media) created by the leaching out from the film of a water-soluble component

- transport of drug through a hydrated, swollen film as the result of the presence in the coating of a water-soluble component (usually high-molecular weight) that cannot be readily leached out
- transport of drug through flaws in the membrane (often present as stress-induced cracks in a coating of low mechanical strength)[9]
- transport of drug through pores that result from incomplete coalescence of a coating prepared from an aqueous polymeric latex

Coating Formulation

The membrane formulation for a reservoir system will have a major impact on membrane structure and thus will greatly affect the performance of the final product.

It is critical that the formulation chosen yields a coating whose properties remain little changed throughout the life of the product. Consequently, we have to be concerned with mechanical properties of the polymer and how these are impacted by additives such as plasticizers and fillers.

The presence of leachable ingredients can be counted on to change the permeability characteristics of the coating.

Effect of Ethylcellulose

Pharmaceutical grade ethylcellulose is available from two manufacturers (Dow Chemical and Hercules) and in various viscosity (or molecular weight) grades. In addition, there are two commercially available forms of aqueous ethylcellulose dispersions (Surelease and Aquacoat).

While there is little reason to believe that the two manufacturing sources of ethylcellulose do not essentially provide similar material, the various grades available (from each supplier) may not be exactly comparable and may produce coatings with subtly differing properties. Consequently, the formulator needs to evaluate material (of equivalent grade) from each source before assuming that material from one source can be substituted for that of the other.

The impact of molecular weight of a particular grade of ethylcellulose on ultimate drug-release characteristics does require careful attention. The effect of varying molecular weight has been described

by Bogelund[10]. More recently, Rowe[9] has demonstrated that the behavior of sustained-release film coatings containing ethylcellulose is directly affected by molecular weight of the polymer used. He postulated that the faster release rates of drug obtained when using low molecular weight ethylcellulose can be linked to flaws created as a result of internal stress that develops in the coating on drying. As the molecular weight of the polymer is increased, the coatings become more resistant to the effects of this stress, and above a certain molecular weight (approximately 35,000), any additional increase in molecular weight has no further effect.

The performance of ethylcellulose coatings obtained from aqueous dispersions may vary as the result of differences in:

- the molecular weight grades of ethylcellulose used
- methods of manufacture
- the additives present
- the manner in which plasticizers are incorporated

Effect of Additives

Plasticizers - Plasticizers are used to increase the flexibility of the coatings and facilitate

coalescence of those coatings produced from aqueous latex systems.

Rowe[9] has demonstrated the benefits of incorporating suitable plasticizers into film coatings produced from organic-solvent-based solutions of ethylcellulose, while Goodhart, et al[11] have discussed the same for an aqueous ethylcellulose pseudolatex. In each case, the selection of appropriate plasticizers helped to improve the barrier properties of the ethylcellulose coatings, resulting in a reduction in release rate of the drugs concerned.

Water-Soluble Additives - Water-soluble ingredients are usually incorporated into sustained-release, film-coating formulations to increase the rate at which drug is released.

Use of Water-Soluble Polymers - The benefits of using water-soluble polymers (such as hydroxypropyl methylcellulose) in conjunction with ethylcellulose has been well documented[12,13]. It is interesting to note, however, that recent information[14] suggests that while hydroxypropyl methylcellulose and ethylcellulose may have a limited degree of miscibility, they may be incompatible. An example of the effect of incorporating a water-soluble polymer (methylcellulose) into

an aqueous latex coating system on ultimate drug release is shown in Fig. 2.

The incorporation of water-soluble polymers into aqueous ethylcellulose dispersions can be critical. Unlike when using organic solvent-based solutions of polymer, a water-soluble polymer introduced into the aqueous ethylcellulose dispersion will mainly be distributed throughout the continuous, aqueous phase. This means that when the coating is dried, the water-soluble polymer will be located at the interfaces between latex particles and may hence interfere with full coalescence of the film. This is especially problematic when using higher levels of the water-soluble polymer as shown by Miller and Vadas[15], where initial coalescence of the coating can be incomplete, and further gradual coalescence may be very much time dependent.

Use of Low Molecular Weight Water-Soluble Additives - Again, the purpose of using such additives is to increase the permeability of the ethylcellulose coating. Such additives might include sucrose, sodium chloride of various surfactants. The use of discrete particulate matter dispersed in organic-solvent-based solutions of ethylcellulose can produce interesting results, since a macroporous membrane can be

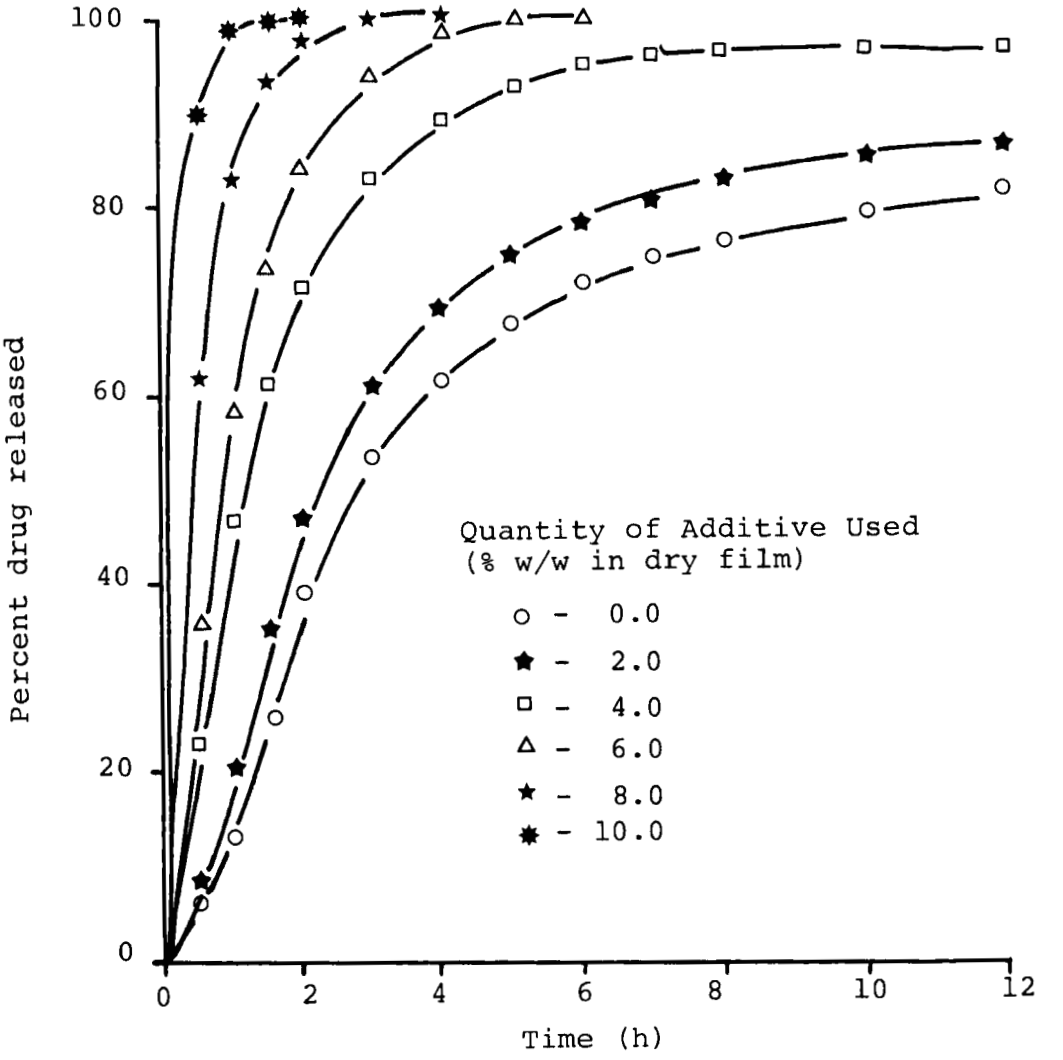


FIGURE 2
Effect of addition of water-soluble polymer (methylcellulose 15 cP) to an aqueous ethylcellulose dispersion (Surelease®) on release of chlorpheniramine maleate from beads coated (10% weight gain) with that aqueous dispersion

created[16]. If such powdered material is used with aqueous coating systems, dissolution of the additive would result in the pores being very small in size.

Surfactants can also be used to increase the rate at which drugs permeate ethylcellulose film coats[16,17,18]. The use of ionic surfactants (such as sodium lauryl sulfate) has also been shown[19] to increase the effect of dissolution pH on drug release from products coated with aqueous dispersions of ethylcellulose.

Use of Insoluble Fillers - Fillers are typically employed with sustained-release film coatings either to reduce tackiness (that occurs during the application of aqueous polymeric dispersions) or to impart color.

When a polymer is dissolved in a solvent, the presence of insoluble fillers generally seems to reduce the permeability of the membrane (as long as the critical pigment volume concentration is not exceeded). With aqueous latex coating systems, however, it is critical to ensure that pigmentation does not significantly interfere with the film-formation process.

Nature of the Substrate

Controlled-release film coatings can be applied to various substrate forms (tablets, granules, spheroids, drug crystals and drug/ion exchange resin complexes).

The nature of the substrate (the formulation and drug used) can be expected to have a signficant effect on the behavior of the final coated product.

Nature of the Drug - All other things being equal, the solubility of the drug and effect of pH on drug solubility, will affect the rate at which the drug is released. In addition, if the molecular weight of the active ingredient is very high, it may be impossible for it to diffuse through the membrane. The influence of the drug itself on release from drug-laden non-pareils coated with an aqueous latex system is shown in Fig. 3.

Size and Shape of the Substrate - Geometry plays an important part in drug release from coated dosage forms. For a given formulation, varying the particle size (of the material to be coated) will dramatically affect the surface area to be covered by the coating, resulting in a variation in coating thickness when a fixed weight gain is used throughout, and thus influencing the rate at which the drug is released (Fig. 4).

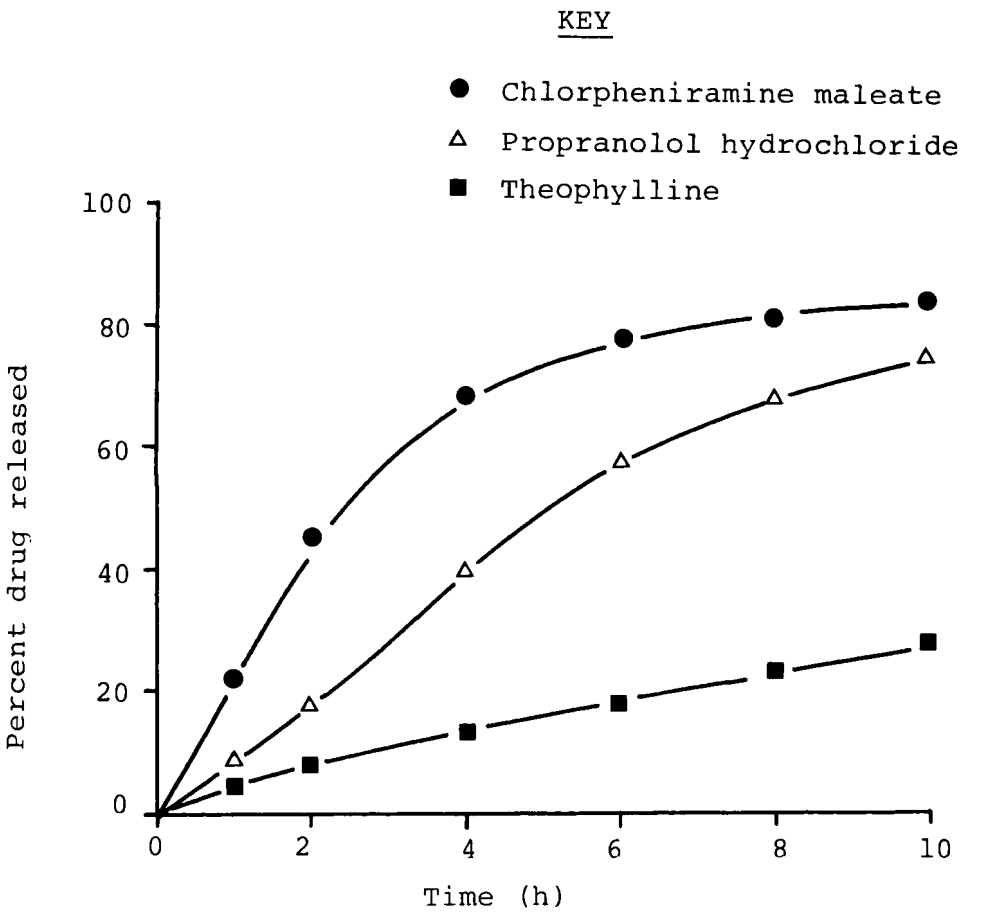


FIGURE 3
Influence of nature of drug on drug release from beads coated (10% weight gain) with an aqueous ethylcellulose dispersion (Surelease®)

Surface area variations can also occur as the result of differences in surface roughness, with the result that drug-release rate can again be affected[20]. The influence of surface roughness (of the drug-loaded substrate) on ultimate drug-release rate is shown in Fig. 5. In this case, Sample A was shown (by

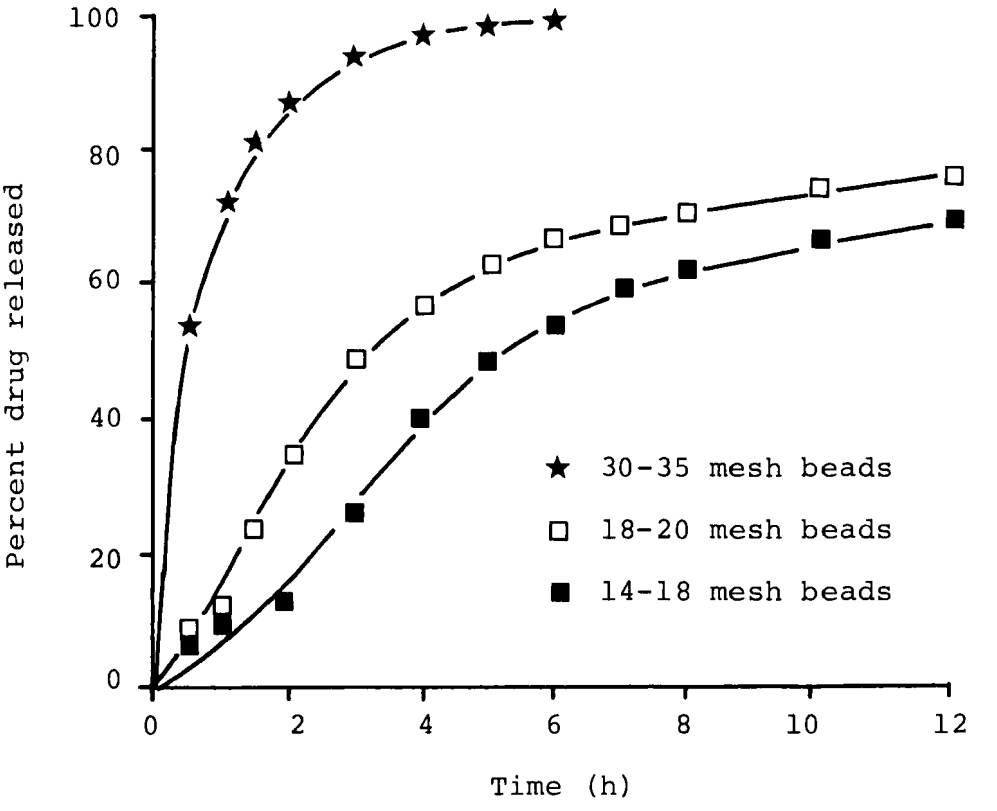


FIGURE 4
Effect of bead size on release of chlorpheniramine maleate from beads coated (10% weight gain) with an aqueous ethylcellulose dispersion (Surelease®)

scanning electron microscopy) to have a significantly rougher surface than Sample B prior to coating.

Presence of Adhesives/Binders - One of the most common approaches utilized in the preparation of oral controlled-release dosage forms is application of drugs to the surface of non-pareils. In these

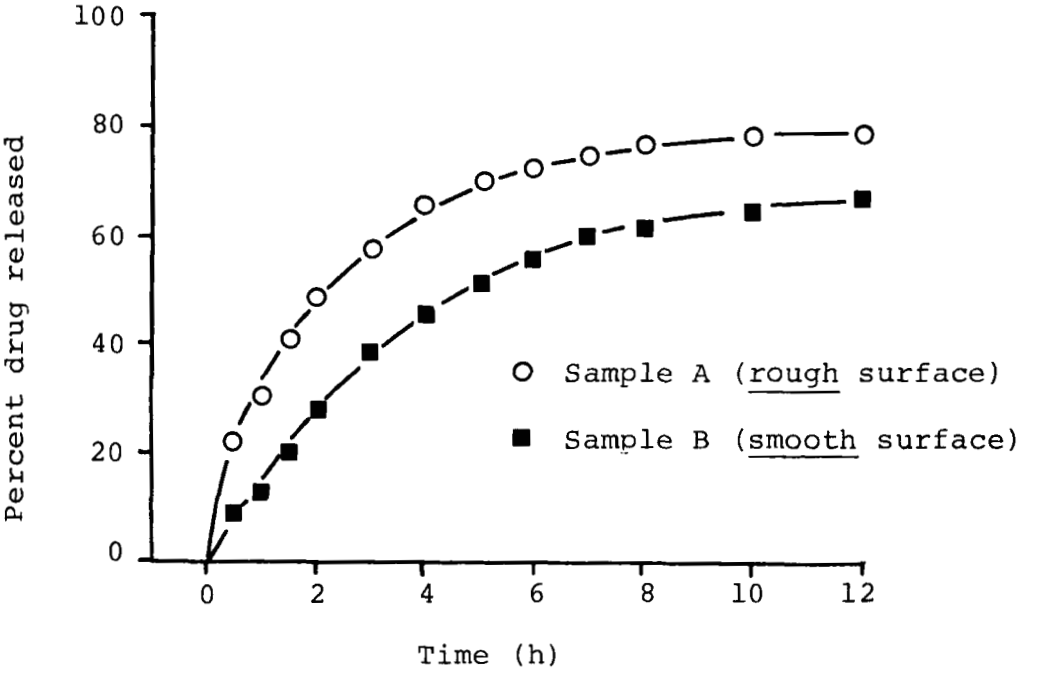


FIGURE 5
Influence of surface characteristics of substrate on release of chlorpheniramine maleate from beads coated (10% weight gain) with an aqueous ethylcellulose dispersion (Surelease®)

situations, it is often essential to use a binder to "fix" the active to the surface of the carrier. The use of such binders may have an effect on the performance of the final dosage form. If the material employed as a binder does not have good adhesive properties, or if the concentration at which it is employed is too low, attrition during processing may cause some of the drug to be liberated from the

substrate and subsequently deposited in the rate-controlling membrane. Such lack of control of distribution of the drug in the final dosage form may affect performance.

The binder may also exhibit other characteristics that ultimately affect drug-release characteristics[21].

Use of Seal Coats - The idea of applying a polymer seal coat to the substrate prior to application of the controlled-release coating is certainly not new, although at the same time, it is not approach that is widely practiced.

The use of seal coats has, however, been recently demonstrated[27] to provide some benefit, particularly when coating drug-laden beads. The presence of a seal coat usually retards release of the drug, particularly when the drug is highly water-soluble and the rate-controlling membrane is derived from an aqueous latex coating system. The results obtained may possibly be explained by:

- reduction in brittleness of the drug layer, thus reducing abrasion problems in the early stages of application of the controlled-release coating
- sealing off surface irregularities that may give rise to variation in surface area of the substrate form

- preventing the premature dissolution of drug (by water in the aqueous polymeric dispersion) that ultimately causes drug to be freely distributed throughout the controlled-release membrane
- reducing substrate porosity that may influence film formation with a latex coating system

Osmotic Effects - The use of osmotic pressure in determining drug-release rate from reservoir controlled-release products has been well documented, and, in fact, certain types of formulations are specifically designed to rely on osmotic pressure to accurately control drug-release rate (for example, the elementary osmotic pump[23]).

With simpler systems (such as film-coated beads), however, the impact of osmotic effects is often overlooked. When we consider the influence of ingredients (for example, excipients such as sucrose or actives such as potassium chloride) used in the preparation of the core to be coated, we should not be surprised to see that osmotic pressure can influence the results obtained[24].

Processing Factors

The structure of a controlled-release film coating will be as much dependent on the process as it is the coating formulation.

The main goal is to design a process that can facilitate the application of a coating uniformly across the surface of material to be coated, and to do so in a manner that is highly reproducible from batch to batch and avoid the introduction of flaws (for example, stress cracks or pick marks) that might interfere with the integrity of the final coating.

Consequently, we should be aware of those processing factors that can affect the results we get, for example:

- What is the effect of the type of equipment chosen (e.g. fluid-bed processes vs. coating pans)? Some of these effects have already been described[20,25].
- What factors affect uniformity of distribution of the coating (e.g. atomizing air pressure, coating dispersion solids, spray rate, mixing efficiency)?
- What influence do the drying conditions in the process have on ultimate performance? We must be concerned, when using organic

solvent-based coating solutions, with avoiding over drying (where spray drying can lead to the formation of highly porous films) or overwetting (where picking could be a problem).

When dealing with aqueous latex coating systems, drying conditions (particularly heat) might greatly influence the coalescence process and determine whether curing processes need to be employed. While the need for a curing step (when using aqueous latex coating systems) has recently been demonstrated[26], the data shown in Fig. 6 suggest that such curing may not always be necessary. This conflicting information may suggest that a better understanding is needed of the critical processing factors involved in the successful application of controlled-release film coatings from aqueous latex formulations.

Overdrying while latex systems are being applied generally means that product temperatures may reach a level where tackiness of the coating becomes a problem. Such tackiness may be reduced by inclusion of appropriate additives (talc, fumed silica) in the coating. Conversely, overwetting may cause drug to be leached from the core material, a result that can affect drug-release characteristics. Such an affect

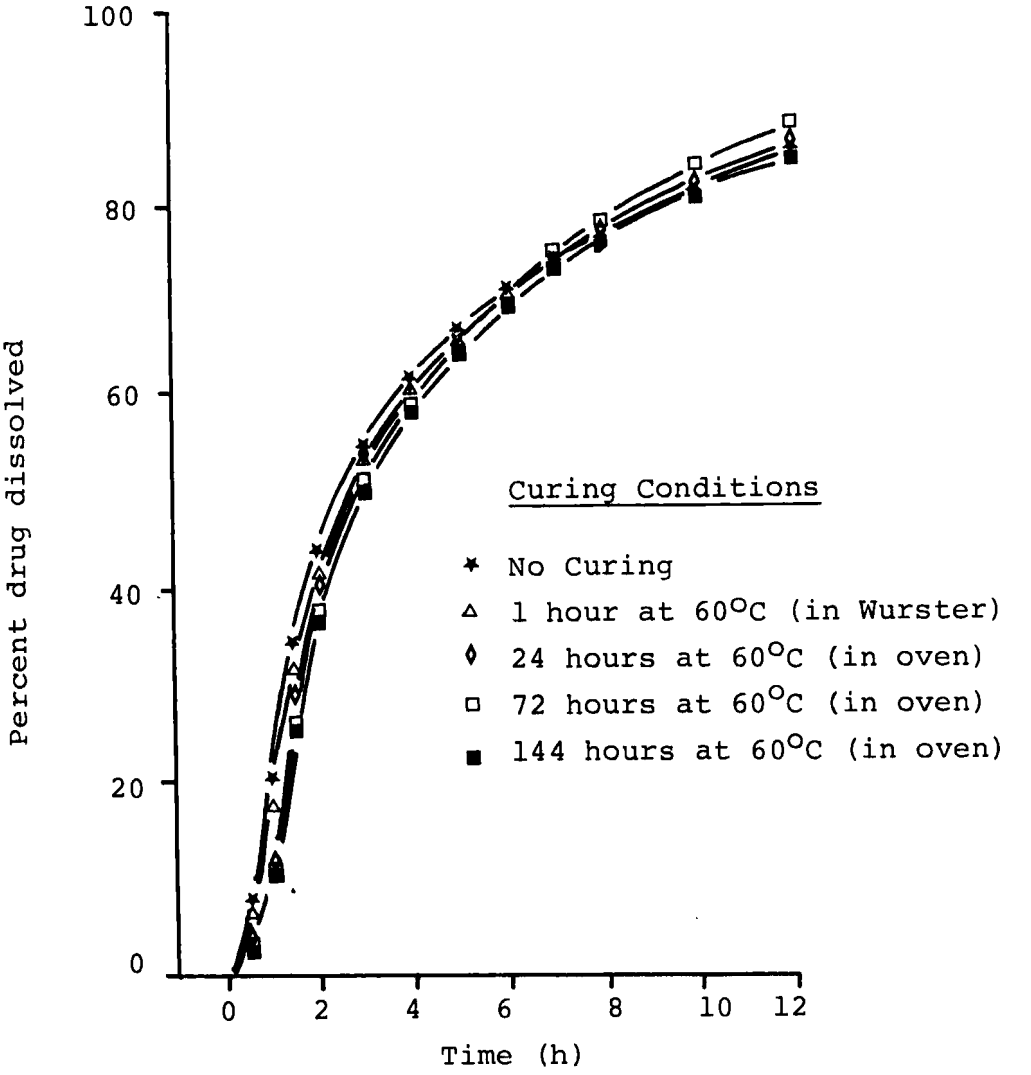


FIGURE 6
Effect of curing on release of chlorpheniramine maleate from beads coated (10% weight gain) with an aqueous ethylcellulose dispersion (Surelease®)

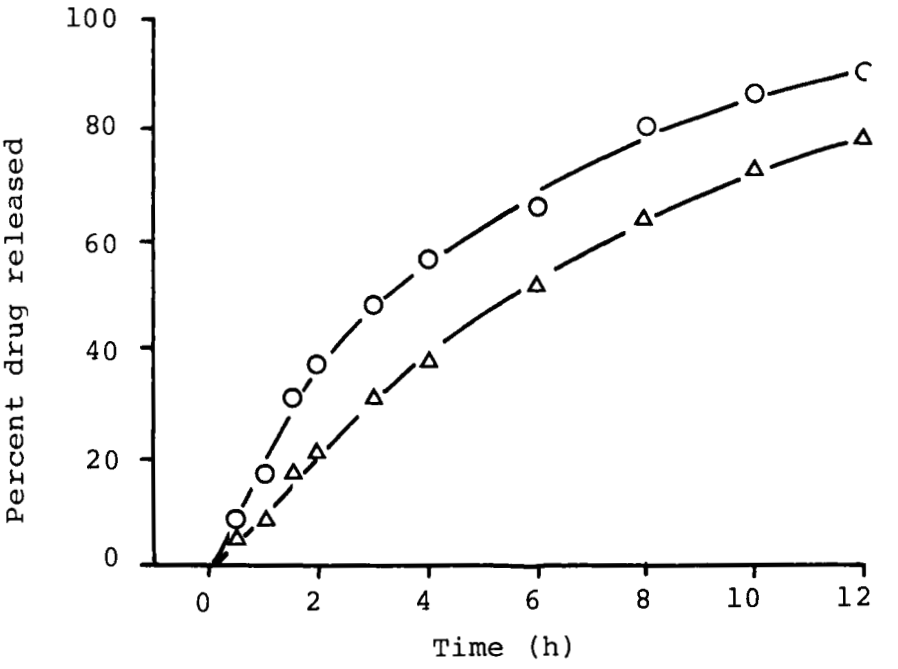


FIGURE 7
Effect of drug leaching (from substrate during coating) on release of propranolol hydrochloride from beads coated (10% weight gain) with an aqueous ethylcellulose dispersion (Surelease®)

is demonstrated in Fig. 7, where the faster release associated with Sample 1 resulted from drug being leached from the core and deposited on the surface of the final coated product.

CONCLUSION

Ethylcellulose has properties that make it very suitable to be used as the main film former in film

coatings that are applied for controlled-release purposes. Both organic-solvent-based and aqueous film-coating methodologies can be employed.

As with any pharmaceutical process, however, there are many critical factors that can influence the results obtained. Since precision is a major objective with controlled-release formulations, many of these critical factors must be examined more carefully if our expectations are to be met.

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