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# Properties of Film-Formers and Their Use in Aqueous Systems

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**Abstract:** For the manufacture of film tablets a variety of polymers with different properties are used in organic and aqueous systems. In the present review, the most important film-forming agents and application systems are discussed with regard to their chemical qualities and physical formulation properties. Furthermore, general phenomena and differences among these agents are illuminated by means of models from macromolecular chemistry.

## Film Formation

Film-formers are polymers capable of hardening to coherent films. In addition, they require chemical structures in their molecules that provide a given solubility in certain media. The physical property of these polymers essential for coating is the ability to form films. How does this kind of film formation occur?

All coating materials used so far in the pharmaceutical industry are physically drying preparations. During the drying procedure either the solvent evaporates from the dissolution or the water evaporates from the dispersion or dissolution. Here the polymers first are present as isolated coils. If the solvent evaporates slowly, the coils approach until, at a certain polymer concentration, they begin to penetrate each other. This concentration is identical with the reciprocal value of intrinsic viscosity.

$$\lim_{c \to o} \left[ \frac{\Delta^{\eta}}{\eta_o} \right] = [\eta]$$

A film is allowed to form provided the individual sprayed droplets are able to coalesce in any one flowable state to permit the macromolecular coils to penetrate each other. For this it is necessary that at least segments of the coils be mobile, i. e. they must be present above the glass transition temperature.

Like the polymer coils the particles of a dispersion may also approach each other. Depending on the temperature, the latex particles either aggregate through additives (emulsifying agents, protective colloids) or they adhere directly to each other.

The penetration of the macromolecular chains and the resulting properties of the film are best illuminated by the differentiated network model shown in Fig. 1.

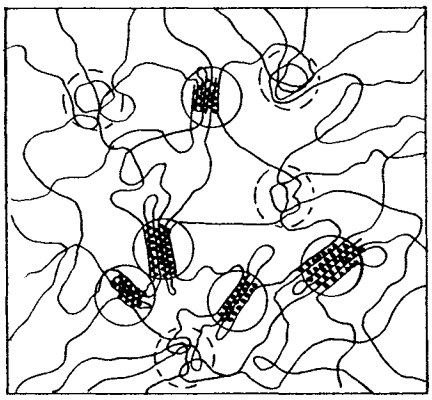

**Fig. 1** Differentiated network model of polymers (1).

Here, the polymer or the film, respectively, is thought to be composed of an uninterrupted entanglement of coiled molecular chains. In this network two areas can be distinguished:
1. ordered, crystalline areas;
2. amorphous areas in which several chains form a loose coil stabilized by weak forces only. If a mechanical strain is applied above the glass transition temperature, i. e. at a temperature at which segments of chains become mobile, these coils will loosen slowly, the chains gliding past each other. Penetration is thus rendered possible. These amorphous areas show more or less appreciable variations in the distribution of free volume, which are characterized by a lack of major intermolecular forces.

The overall behavior of the film depends on the mesh size of the network and on bond strength, but above all on the degree of entanglements. If no amorphous areas form but only ordered structures, this will very easily result in domain formation and thus cracking, orange peel, etc.

Besides the capacity of penetration, film-formers must present a certain adhesiveness to the material to be coated. The adhesion to the dosage form and, in the further course of the coating process, to the polymers themselves, depends on the chemical and physical interactions between polymers, plasticizer, solvent and surface as well as on diffusion phenomena. To put it more simply, the surface properties and energies of dosage form and coating material, their interfacial tension, geometry of the cores, viscosity of the solution, substances absorbed in the dosage form, such as water, etc.,

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play a role here. Adhesion can, for instance, be determined and optimized by means of contact angle measurements (2). Interactions between the polymers and the solvents can be approximately predicted by determining their solubility parameters (3, 4). Like thermal analytical processes, this concept can also be employed for optimizing the use of plasticizers (5–7). However, the measurement of the glass transition temperature is preferable for this purpose.

Optimizing the entire system of application consisting of polymer, plasticizer, solvent or dispersing agent, respectively, and other additives by the above-mentioned methods is of great theoretical interest. However, in practice, basic formulations exist for the most commonly used film-forming agents, which contain quanti- and qualitative specifications of these substances. Therefore, this subject will not be discussed in more detail in the present paper.

In addition to the properties mentioned so far that all coating materials should have in common there are special requirements that coating substances for drugs ought to satisfy. The number of suitable substances is hereby automatically reduced to the few film-formers in common pharmaceutical use. These are as follows:

*Cellulose Derivatives*

Soluble in water: methylcellulose (MC), hydroxyethyl cellulose (HEC);
Soluble in water and organic solutions: hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC);
Soluble in alkalies: cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), carboxymethyl ethylcellulose (CMEC), hydroxypropyl methylcellulose acetate succinate (HPMC-AS);
Soluble in organic solutions only: ethylcellulose (EC).

*Polymethacrylate Copolymers*

Soluble in acids: Eudragit® E;
Soluble in alkalies: Eudragit®L, Eudragit®S;
Soluble in organic solutions only: Eudragit®RL, Eudragit®RS.

*Further Substances*

Soluble in water and organic solutions: polyvinyl pyrrolidone (PVP);
Soluble in alkalies: polyvinyl acetate phthalate (PVAP).

*Natural Coating Materials*

Shellac, waxes.

## Water-Soluble Film-Formers

Water-soluble polymers, cellulose derivatives in particular, are used to protect the dosage form from environmental influence and to improve its appearance, ingestion, taste, etc. Since a wide variety of coating devices are presently available, the application of the film-formers to the dosage form poses no problems. All cellulose ethers form transparent elastic films at least with plasticizers. Their suitability for film formation depends on the structural relationship between cellulose ether and cellulose and on the solubility of the cellulose ether.

The polymers available, such as hydroxypropyl cellulose, hydroxyethyl cellulose and hydroxypropyl methylcellulose and other cellulose ethers as well as polyvinyl pyrrolidone, need not necessarily be plasticized. If required, for instance with very sharp edges, propylene glycol and polyethylene glycol, among others, may be used as plasticizers.

Film-forming agents giving solutions of low viscosity are the most suitable ones for use. Also, it is generally accepted that a correlation exists, inter alia, between the degree of viscosity of a film-former and its tendency to tackiness (8, 9). For film-coating, therefore, types with a viscosity of 3–15 mPas in 2 % solution ought to be used. Above this level sticking creates problems and spraying is more complicated. Below this range, in turn, the polymer chains shorten to such an extent that the stability of the film is affected, i. e. film strength decreases too much and the phenomenon of internal stress arises.

In summary it may be stated that hydroxypropyl methylcellulose in types 3–6 mPas (2 % solution) seems to be at present the most suitable and technologically most unproblematic water-soluble film-former.

## Internal Stress

As with sugar-coated tablets, cracking and splitting of the coat may also be encountered with film tablets and other coated dosage forms. They occur in the form of cracks visible to the eye or as craizes identifiable only under the microscope. These may affect the appearance of water-soluble films and the drug release from controlled-release coatings, i. e. the gastric juice resistance of enteric film coatings.

This instability is caused primarily by the so-called internal stress. Explanations for its origin are, however, based more on experimentation and are difficult to underpin theoretically (10–13).

Internal stress can be due to shrinkage of the film on evaporation of the solvent and to the different thermal extension of film and core. The shrinkage of the film plays a major role. The polymer chains are sufficiently mobile to flow as long as the film-former is present in solution or swollen form. When the solvent evaporates, there is a decrease in volume in the applied coating and thus a reduction in the thickness of the coating layer. If the amount of solvent evaporated is so large that polymer chain mobility becomes insufficient, the film can no longer resist, by flow processes, a further volume reduction caused by drying; as a result internal stress develops. Understandably, the magnitude of internal stress depends on interaction phenomena and thus on the overstructure of the polymer. This, in turn, is dependent on the degree of polymer elasticity, the evaporation rate of the solvent and the solvent that is the last to be retained in the film. Moreover, internal stress is related to the glass transition temperature of the film. The higher the amount of plasticizers added to the film (which is likely to reduce the glass transition temperature), the more the chain mobility is increased and the internal stress diminished (10, 11).

The same behavior applies to Young's modulus of the film; here a linear correlation is proposed to exist (11). In the build up of internal stress, film pigmentation is also a factor to be considered (10, 11). Moreover, internal stress increases with film thickness, too (10).

The stress itself also influences the adhesion of the film to the core. It is common knowledge that adhesion decreases as the wettability of the tablets is reduced through the employed coating material and elevated internal stress. When the stress exceeds the tensile strength of the film, cracking occurs. In certain instances phase transition phenomena should also be taken into account.

Solvents, too, have a marked effect on internal stress. The thermodynamically better the solvent dissolves the film-former, the higher will be the internal stress in the film. This is

explained by the fact that a solvent with good thermodynamic qualities, i. e. with a solubility parameter close to that of the polymer, is more able to widen the polymer coils by interacting with the polymer. The solvent that minimally dissolves the polymer produces the smallest coil dimensions. With a thermodynamically good solvent, therefore, the decrease in volume is more appreciable than with a poor one, and hence internal stress is greater (11). This explanation frequently found in the literature, however, can be challenged. No matter whether one uses a good or poor solvent, there is always a critical concentration at which penetration of the polymer coils starts. This concentration is identical with the reciprocal value of intrinsic viscosity. The volume reduction itself becomes critical only when the amount of solvent evaporated is large enough to prevent the chains from flowing. This dependence found empirically can only be explained by additional kinetic effects or the presence of multicomponent systems in coating solutions. These multicomponent systems easily result in phase separations on film formation or evaporation of the solvent, respectively, and thus in overstructures and internal stress.

## Pseudo-Latex Dispersions

In addition to solutions, film-formers may be available as latex dispersions. A characteristic of these dispersions is that the film-formers are present in the latex particles only, namely in a smoothened, elastic rubbery form availed of in pharmaceutical coating. Owing to the arrangement in dispersed droplets, the viscosity of the preparation is affected to a lesser degree than in solutions, so that considerably higher concentrations can be used. The formation of a film can take place in two different ways, depending on the temperature. Above the minimum film-forming temperature the droplets flow more or less strongly together, thus building up a film. Below this temperature the structures of the latex particles are maintained in the film, as the latex spheres only cohere at the surface (14).

One distinguishes between the so-called "genuine" latex dispersions made from monomers by emulsion polymerisation and the so-called pseudo-latex dispersions. For the production of pseudo-latex dispersions available polymers are employed. These can be softened by plasticizers and water until the polymer particles are dispersed to yield latex particles, or the film-former is dissolved together with a plasticizer, a relatively large amount of surfactant is added, the solution is dispersed in water and the solvent then evaporated.

Hydroxypropyl methylcellulose is available as two pseudo-latex preparations. i. e. Sepifilm® and Opadry®.

Sepifilm® is a powdery mixture from a low-substituted, low-viscosity hydroxypropyl methylcellulose with about 10 % polyethylene glycol 400 stearate as plasticizer and dispersing agent. This pseudo-latex dispersion is based on the principle that polyethylene glycol 400 stearate is not water-soluble but dispersible, enveloping the hydroxypropyl methylcellulose in dispersion droplets.

Opadry® is a powdery mixture containing hydroxypropyl methylcellulose, polyethylene glycol 400 and pigments. Both ready-for-use products are prepared simply by stirring the powder in water and allowing the mixture to swell for 30–60 minutes. The resultant pseudo-latex dispersions permit an unproblematic use with a relatively high content (15–18 %) of dry substance for a hydroxypropyl methylcellulose preparation.

## Water-Insoluble Film-Formers

Naturally, it has so far been customary to dissolve the water-insoluble polymers in organic solvents and spray them onto the dosage form using a suitable device. When a film-former is dissolved in an appropriate organic solvent, practically no complications should be expected. But since these solvents not only are toxic but also to some extent explosive and dangerous, their discharge into the air being drastically restricted by legislation, attempts have been made to eliminate organic solvents from coating formulations. Some of the most commonly used methods are presented in Table I and discussed below.

Eudragit®E 100 (powder) and Eudragit®E 12.5 (12.5 % solution in isopropanol/acetone 60:40) are soluble in common organic solvents and gastric juice. For coating purposes anti-sticking agents and dyes, if necessary, are added to a solution of the polymer. The solution or suspension, respectively, then is sprayed. However, this substance is not commercially available as an aqueous preparation. Although it is obtained by emulsion polymerization, and even if a latex dispersion were the preparation of choice, it is not possible to apply the latex particles of this polymer in a stable, film-forming state to the dosage form. The minimum film-forming temperature would be above 70°C with this dispersion, so that the latex particles could only aggregate at the surface, being unable to form a film. Therefore, the latex dispersion of the Eudragit®E range,

**Table I.** Water-insoluble film-formers and their formulations

| Film-former | Formulations | | | | | | |
|---|---|---|---|---|---|---|---|
| | Organic solution | Water-alcohol mixture solutions | Ammonium salts | Coating emulsion | Latex dispersion | Thermal gelation | Redispersion |
| Eudragit®E | + | – | – | + | – | + | – |
| Eudragit®E 30 D | + | – | – | + | + | – | – |
| Eudragit®L | + | – | – | + | – | – | – |
| Eudragit®L 100-55 | + | + | – | + | + | + | + |
| CAP | + | – | – | + | – | – | – |
| HPMCP-55 | + | – | – | + | – | + | – |
| HPMCP-50 | + | – | + | + | – | + | – |
| HPMC-AS | + | + | – | + | – | + | – |
| CMEC | + | + | – | + | – | + | – |
| Ethylcellulose | + | – | – | + | + | – | – |
| PVAP | + | – | – | + | – | + | – |

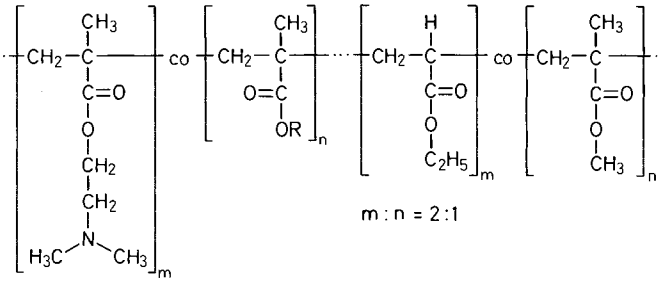


**Fig. 2** Chemical structure of the various preparations of the Eudragit®E range.
Poly(butyl methacrylate, (2-dimethylaminoethyl) methacrylate, methyl methacrylate) 1:2:1
(Eudragit®E 100, E 12.5)
Poly(ethyl acrylate, methyl methacrylate) 2:1
(Eudragit®E 30 D)

Eudragit®E 30 D, contains another polymer (Fig. 2). This substance does not dissolve in gastric juice because of a lack of functional groups. Therefore, Eudragit®E 30 D acts as a diffusion membrane.

To obtain coatings possessing the same disintegration time as those provided by Eudragit®E 100, the addition of hydrophilic polymers, such as 10 % hydroxypropyl methylcellulose, is necessary. It should be noted that tablets with these coatings are, upon storage, prone to prolongation of their disintegration time.

Ethylcellulose also acts as a diffusion membrane. Using organic solvents, it can be easily applied to the dosage form. A mixture of acetone/isopropanol or ethanol, respectively, is the most suitable solvent for this purpose. Better films can be obtained with phenols or toluene, but these solvents are, of course, less appropriate in practice. The drug release through the ethylcellulose membranes can be controlled by the thickness of the coating layer, hydrophilic additives and plasticizers. Purely aqueous preparations cannot be produced with ethylcellulose; however, an aqueous pseudo-latex dispersion, called Aquacot®, is commercially available. Its manufacture requires a large amount of sodium lauryl sulfate as an emulsifying agent.

Nevertheless, Aquacot® provides timed-release coatings. The coatings afforded by this product are less recommended as diffusion membranes for tablets. They are, however, more suitable for pellets.

Further diffusion membranes are Eudragit®RL and Eudragit®RS, which can only be applied from organic solutions. With these products, drug release has to be controlled by the thickness of the film coating. Available enteric coating materials also include cellulose derivates and polymethacrylic acid derivatives and polyvinyl acetate phthalate.

The simplest way of avoiding the use of organic solvents would be the application of a mixture of water and alcohol that is suitable for two new film-formers. One of these is carboxymethyl ethylcellulose, a novel cellulose ether. It dissolves in 60 % ethanol and 70 % isopropanol and requires 2 % triacetine as a plasticizer. On the basis of our investigations, it offers ease of application, giving solutions of very low viscosity. The other film-former soluble in a mixture of water and alcohol is hydroxypropyl methylcellulose acetate succinate, currently under study. It dissolves in 60 % acetone, 50 % methanol, 50 % ethanol and 50 % isopropanol. Since it is highly elastic, no plasticizers are needed. On the other hand, of all cellulose esters it shows the highest water vapor permeability. These two film-formers come in three types each, which dissolve above pH 5, pH 5.5 and pH 6.0, respectively. As carboxymethyl ethylcellulose is free from ester groups, it is particulary suitable for the coating of enzyme preparations. With these drugs, separating coatings had to be applied to prevent the enzymes from affecting the stability of esterified film-formers by "digestion".

Like Eudragit®E, the gastric juice resistant Eudragit®L is also available in various types. Eudragit®L 100 (powder) and Eudragit®L 12.5 (12.5 % solution in isopropanol) are too hard and brittle to be used in a latex dispersion. Moreover, with this dispersion the minimum film-forming temperature would be above 70°C. Thus, their structure had to be changed; 70 % of the methyl methacrylate fraction was replaced by ethyl acrylate (Fig. 3), which reduces polymer branching. As a result, the minimum film-forming temperature decreases to 27 °C, and a film is allowed to form. Yet, this modification of the polymer structure also affects some properties of the resultant film tablet, such as disintegration and drug release (2, 15). For instance, there is a decrease in the critical *in vitro* pH-dissolution range, i. e. the pH range in which the film coating begins to dissolve, from 5.9–6.0 (Eudragit®L 100 from organic solution) to 5.0–5.8 (Eudragit®L from Eudragit®L 30 D). Drug release from the film tablets increases similarly (2, 15). To cope with the situation, manufacturers have recently developed a further coating material of the Eudragit® range, Eudragit®L 100-55. This polymer is the dry substance of Eudragit®L 30 D; it begins to dissolve already at pH 5.5.

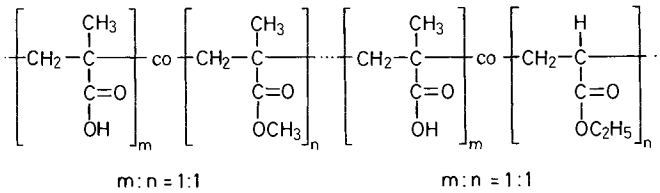


**Fig. 3** Chemical structure of the various preparations of the Eudragit®L range.
Poly(methacrylic acid, methyl methacrylate) 1:1
(Eudragit®L 12.5, L 100)
Poly(ethyl acrylate, methacrylic acid) 1:1
(Eudragit®L 30 D, L 100-55)

The third possibility of obtaining aqueous preparations is to use ammonium salts. They are made from aqueous solutions of gastric juice resistant polymers, which were neutralized with ammonia to permit dissolution of the polymers in water as salts.

Under coating conditions the ammonia of these salts is allowed to evaporate, and the insoluble enteric film remains on the core. From the swelling number (% uptake of gastric juice by the tablets) (15) the conclusion can be drawn that this procedure actually does not provide gastric juice resistance. As the films are very thick, there is not enough time during the 2-hour test of gastric juice resistance for the gastric juice for penetration. Thus the film tablets do not disintegrate during the

observation period, which could give the impression that the enteric tablets are unaffected. On close examination it becomes clear, however, that the tablets do not disintegrate but are in fact swelling too much, and hence the active substances are not protected from gastric juice.

A further possibility of avoiding organic solvents is the use of coating emulsions (16). Advantages of these preparations are that 75 % less solvent is needed and that the same film composition as from an organic solution is retained on the core. Since ethylene glycol monoethyl ether used as a solvent also has properties similar to those of an emulsifier, it is highly tolerant of plasticizers. As all plasticizers can thus be employed, these coating emulsions are most reasonably used in cases where a change from organic solutions to more aqueous preparations is not supposed to alter the resulting film.

A more recent method to eliminate organic solvents is the application of finely ground, micronized film-formers that are insoluble in water, yet capable of film formation. The method is called thermal gelation (17). It is to be understood as a procedure utilizing suspended film-formers,plasticizers and temperature for film formation. The film-forming agent must be present in an extremely fine form. Here triethyl citrate ought to be used as a plasticizer with exactly defined, bilateral properties of solubility. On the one hand, the entire amount of plasticizer should be in solution as long as the prepared suspension contains an excess of water. In this way softening of the film-former, coagulation, and clogging of the atomizing nozzles can be avoided. On the other hand, when most of the water is evaporated, the affinity of the plasticizer for the film-former should be predominant. The plasticizer is then able to penetrate and soften the film-former, and a film is allowed to form.

During this process, the film-forming polymer, insoluble in water, is first suspended in water or a mixture of water and plasticizer. When suspensions of micronized film-formers, in water and plasticizer, are sprayed onto the cores, the water begins to evaporate. Below the solubility limit of the plasticizer, an unstable transient three-phase system originates, and the plasticizer separates as droplets. Plasticizers with the desired properties of affinity immediately approach the micronized film-former and penetrate it. Hereby the minimum film-forming temperature. i. e. glass transition temperature, is reduced to allow the plasticized particles, under the influence of warm drying air, to build up a film.

The following fine powdery products are commercially available for this purpose: HP 50®-F, HP 55®-F, Eudragit®L 100, Eudragit®L 100-55. The behavior of the finished film tablets coated by thermal gelation differs to some degree from that of tablets made from organic solutions. With the former, the minimum film thickness required for gastric acid resistance is increased. Therefore, the disintegration time of these film tablets is a little longer.

In addition to thermal gelation, the latest process, i. e. the so-called "redispersion", also uses the dry substance of Eudragit®L 30 D. In this process, the film-former is suspended in water and mixed with so little an amount of alkalies or organic base that approximately 6 Mol % of the carboxyl groups are neutralized. This yields a pseudo-latex dispersion which is handled analogously to Eudragit®L latex dispersion (L 30 D).

## Prospects

An adequate number of alternative formulations exist at present for water-soluble film-formers, those dependent on pH for solubility, and agents that are soluble in organic solutions only. By optimum adjustment of the coating methods to the available equipment, it should thus be relatively easy for an experienced manufacturer of film tablets to reproduce coatings with the properties desired, either from aqueous or organic systems.

Recently, in the use of enteric coatings, another problem has come into prominence. As the polymers soluble in the small intestine are esters, except CMEC, they tend to hydrolyze. Studies on ester cleavage (13, 18–20) show that the tendency to hydrolyze is greatly reduced in the CAP-HPMCP-Eudragit® range. Furthermore, there is evidence that hydrolysis can be hastened by the active substances contained in the film or core (18, 20). Therefore, it is quite possible that interactions between coat, core and active substances may affect, during storage, the chemical stability of film-formers and thus their physical properties. Hence it seems that in the future, in close co-operation with the related disciplines, we ought to search for film and membrane formers offering not only ease of application but also the desired properties regarding solubility, diffusion and chemical stability. The development of CMEC apparently represents a big step forwards. Others should follow, since the choice of polymers, especially those suitable as diffusion membranes, is still limited.

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