

**Bauer · Lehmann · Osterwald · Rothgang**

# **Coated Pharmaceutical Dosage Forms**

**Fundamentals, Manufacturing Techniques,  
Biopharmaceutical Aspects,  
Test Methods and Raw Materials**

**medpharm Scientific Publishers**



# Coated Pharmaceutical Dosage Forms

**Fundamentals, Manufacturing Techniques,  
Biopharmaceutical Aspects, Test Methods  
and Raw Materials**

**Kurt H. Bauer, Ph. D.**  
Professor of Pharmaceutical Technology  
Albert-Ludwigs-Universität Freiburg i. Br.

**Klaus Lehmann, Ph. D.**  
Scientific Consultant Pharma Polymers  
Röhm GmbH, Darmstadt

**Hermann P. Osterwald, Ph. D.**  
Managing Director  
allphamed Pharbil Arzneimittel GmbH, Göttingen

**Gerhart Rothgang**  
Formerly Röhm Pharma GmbH, Weiterstadt  
Plant Manager, Responsible Pharmacist (Production)

With 96 figures and 46 tables



CRC Press

Boca Raton Boston London New York Washington, D. C.  
**medpharm** Scientific Publishers Stuttgart 1998

thereby providing stable latex-like systems [81]. For this purpose, 350 ml of demineralized water are given into a one-liter three-necked glass flask, equipped with reflux condenser, high-speed stirrer and contact thermometer, whereupon 150 g of ground polymer are suspended in this water. Stirring is performed at 400 to 1200 rpm, with simultaneous heating to 80 °C. This temperature is maintained for 2 hours and stirring then continued without heating. At the end of the process, milky-viscous, stable dispersions with particle sizes between 15 and 150 nm are obtained [141].

### Dispersion of Polymer Salts

Salt-forming functional groups in polymers show shifting pK values, since each ionic group formed influences the protonation or deprotonation of the neighboring groups, causing the acidity or basicity of the remaining groups to decrease continuously. Salt formation thus extends over a wide pH range. The hydrophilicity increases with the degree of neutralization, and the ionic groups of like charge help to stretch and uncoil the polymer molecules until the polymeric salt dissolves at a particular degree of neutralization. This depends on the content in salt-forming groups and hydrophobic regions, but often occurs at 20 to 60% neutralization. In the transition range, where salt formation has already caused noticeable hydrophilicity in several regions of the polymer molecule without dissolution taking place, dispersion of the polymers may be facilitated and latex-like dispersions be formed which are stabilized by the charges of the ionized groups. This effect of partial neutralization is utilized for redispersing polymer powders [80].

### Redispersion of Dried Latexes

Suitable drying conditions for latexes can be selected to prevent film formation occurring and to obtain isolated latex particles in the

dry powder [48]. Spray drying can even be performed above the minimum film-forming temperature, since the evaporating water strongly cools the spray droplets and the capillary forces responsible for film formation are virtually ineffective. Freeze drying can be used for dispersions from soft polymers with low film-forming temperatures. Under certain conditions, latexes can be reconstituted from dry powders consisting of loose agglomerates of unfilmed, isolated latex particles. This process is aided by emulsifiers and plasticizers, salt formation at the polymer molecule, and use of stirring equipment with controlled shear forces [141].

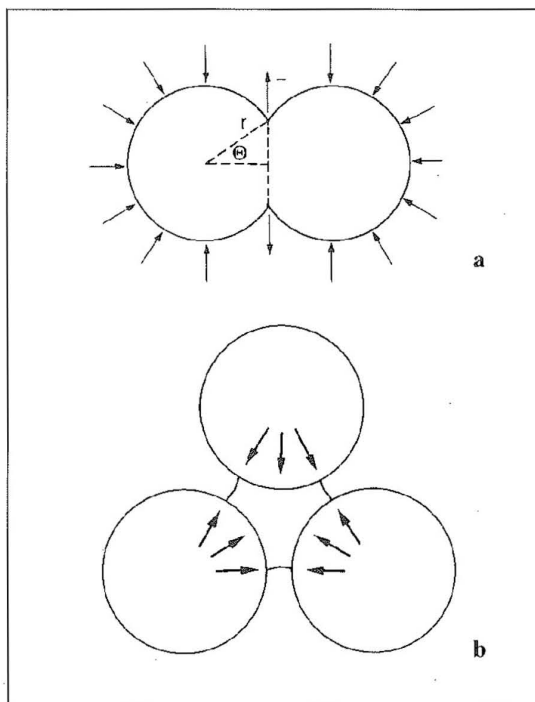
#### 4.2.4.3.3 Mechanism of Film Formation

Polymer dispersions show a special film-forming mechanism. When the dispersing medium water evaporates, the latex particles initially arrange themselves in the closest sphere packing. As drying continues, they flow together, provided the polymer substance is soft enough. This process is termed *coalescence*. At this stage, the remaining water is squeezed out and a water-insoluble, practically homogeneous film is formed.

The driving force for film formation is the gain in surface energy [121], but in the case of these minute spherical latex particles, the capillary pressure which develops on evaporation of the water apparently plays a more important role [67]. According to Laplace this capillary pressure is

$$P = 2\gamma/r$$

where  $\gamma$  is the interfacial tension between water and air, and  $r$  the radius of the particles [122] or the radius of curvature of the concave meniscus [123] (Figure 4-2). If the radius of the dispersed particles is reduced by one order of magnitude, e.g. from 1  $\mu\text{m}$  = 1000 nm to 100 nm, the capillary pressure rises tenfold. This means that the most finely divided dispersions produce the best films.



**Fig. 4-2. Film formation from latex particles**  
**(a) Deformation of the sphere during viscous flow according to Frenkel [121]**  
**(b) Action of the capillary forces according to Brown [123]**  
 $r$  = particle radius  
 $\Theta$  = half coalescence angle

Film formation is disturbed if water is quickly soaked up by a porous surface. This reduces the time span for the capillary pressure required for coalescence of the particles to develop and therefore disturbs the film-forming process. The closer the drying temperature gets to the MFT, the more pronounced this effect is. If the latex particles have formed the closest sphere packing just before film formation, the water content of the layer, which corresponds to the interstitial volume, is only 26%. Therefore, there is less shrinkage during film formation from polymer dispersions than from polymer solutions.

Given skilful processing, films from latex systems are practically pore-free and may even be less permeable than films of the same

composition applied from organic solution. Table 8-2 (p. 193) shows comparative measurements performed in 1982 by List [71, 84], who attributes this effect to the significantly higher density of the latex films. This in turn can be explained by the capillary pressure effective during film formation. In practical use it has been found that less film is required in latex processing, e.g. for producing pellets of chlorphenamine maleate with a sustained-release coating of Eudragit® RS (see Figure 4-4). Owing to the higher solids content of latex formulations, fewer individual layers are normally necessary. If the polymer is not evenly distributed in the spraying process, more latex may, however, be required to obtain the desired controlled-release effect.

With soft polymers and a processing temperature approx. 20 °C above the MFT, film formation from latexes is observed within a few seconds to minutes. However, if the polymers are hard and the processing temperature close to the MFT, it may take several hours or even days. Electron micrographs reveal honeycomb structures in this case [59] as it can also be seen in Figure 4-5a. Subsequent treatment of the films (“curing”) for one to three hours at 60–70 °C has been suggested for EC latexes to assure stable film properties [114]. Curing of coated pellets immediately after the coating process was found to have a significant influence on the drug release profile [138]. Both retardation and enhancement were observed to varying degrees, depending on the type of drug and the curing conditions in the range of 40 to 60 °C and 1 to 24 hours. In the case of soft polymethacrylate latexes with an MFT below 10 °C, film formation may be completed a few minutes after application of the coating formulation (see Figure 4-5 b) [141]. In many cases, watertight film coats already form isolating layers during spraying, so that the cores are immediately sealed against penetration of the dispersing medium water for the remainder of the process. Therefore it is often possible to