15 Membranes in Drug Delivery

Simona Maria Fiorentino, Rossella Farra, Barbara Dapas, Bruna Scaggiante, Federica Tonon, Gabriele Grassi, and Mario Grassi

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15.1 INTRODUCTION
A membrane can be defined as a sheet of solid or semisolid material, insoluble in its surrounding medium, which separates phases that are usually (but not necessarily) fluid [1]. A transport system is realized when there is a passage of solute across the membrane.

Based on mechanisms ruling mass transport, typically, membranes can be divided into two main classes: biological and synthetic membranes. Indeed, while in synthetic membranes the driving force for mass transport is usually represented by the chemical potential gradient, in biological membranes, other driving forces can occur. Facilitated diffusion implies solute binding to a protein embedded in the biological membrane and, then, protein–solute complex permeation through the membrane (this mechanism does not require energy as solute diffusion takes place according to the chemical potential gradient). Important examples are represented by H+/organic cation antiport system and the dipeptide transporter [2]. Active transport denotes carrier transport processes consuming energy since transport often takes place against a chemical potential gradient. The energy required for active transport can be supplied by two different mechanisms: cotransport and ATP pump [3]. In cotransport, the target molecule associates to another compound that crosses the cellular membrane due to the existing concentration gradient (this is the case of glucose and amino acids that associate to Na+ crossing the cellular membrane according to the concentration gradient). In the ATP pump case, instead, the energy required for molecule transport is supplied by the
The case of strong cross-links between polymeric chains (typically chemical covalent bonds), the network does not modify with time. When, on the contrary, weak cross-links prevail (typically physical interactions such as Coulombic, van der Waals, dipole–dipole, hydrophobic, and hydrogen bonding interactions), polymeric chains are not so rigidly connected to each other, and the similarity with the sponge is no longer so pertinent. Indeed, while cross-link density (number of cross-links per unit volume) is constant with time (in static conditions), Brownian motion of chains and segment of chains make the local cross-link density time dependent. As a consequence, whereas average dimensions of network meshes do not modify, each mesh can modify, thus resembling a statistical network. Obviously, this kind of network can easily undergo erosion due to polymer–polymer junction weakness.

This physical frame is made more complex by the fact that the whole structure can be constituted by an ensemble of small matrix domains embedded in a continuum, usually represented by a polymer solution as it occurs for Carbopol [6,7]. Finally, the contemporary presence of two networks (interpenetrating structures), originated by two different polymers, can further complicate the scenario. Typically, these systems are produced by an initial swelling of a monomer and reacting to form a second intermeshing network structure [8,9]. Obviously, the choice of the polymer depends on the final administration route (examples include oral, ophthalmic, rectal, vaginal, and subcutaneous) and on different factors such as membrane swelling degree, biodiversity, biocompatibility, interactions with drug, excipients, and mechanical properties.

Despite the considerable wide application spectrum of membranes, typically, their use in the delivery field falls into drug release modulation on the basis of a diffusive controlled mechanism [10], isolation of particular structures from the external environment [11], making artificial implants biocompatible [12], allowing drug release (due to membrane dissolution) only when particular environmental conditions take place [13], and simulating the permeation properties of natural tissues [14–23]. At this purpose, it is interesting to consider some typical examples taken from the two most important delivery system categories: externally regulated and self-regulated delivery systems [24]. For what concerns externally regulated systems, Miyazaki and coworkers [25] use ethylene vinyl alcohol membranes in reservoir-type drug delivery systems for the release of bovine insulin in the presence of ultrasounds. When diabetic rats receiving implants containing insulin are exposed to ultrasound (1 W/cm² for 30 min), a sharp drop in blood glucose levels is observed after the irradiation. This indicates a rapid rate of release of insulin in the implanted site. The authors attribute this behavior to temperature rising due to the radiating energy supplied.

Okahata and coworkers [26,27], working on thermoresponsive delivery systems, use semipermeable nylon capsules prepared by interfacial polymerization (trimesoyl chloride...
as a cross-linking agent) of ethylenediamine and terephthaloylchloride or 1,10-decanedicarboxylic acid. NaCl-loaded capsules are transferred to dodecane solutions of dialkyl surfactant in order to introduce an amphiphilic bilayer on the capsule membrane. Remarkable permeability changes induced by temperature changes are observed at the phase transition temperature, in contrast to the uncoated capsules. Bae and coworkers [28] working on insulin delivery report the use of thermosensitive hydrogel membranes constituted by poly(N-acryloylpyrrolidine) and its copolymers with styrene or 2-hydroxyethylmethacrylate cross-linked by ethylene glycol dimethacrylate. The cross-linked poly(N-acryloylpyrrolidine) homopolymer shows thermosensitivity in water swelling, with weak mechanical strength, this restricting its practical application to diffusion experiments. The incorporation of a hydrophobic monomer into the polymer improves the mechanical strength and lowers the overall swelling level as well as thermosensitivity. Accordingly, membrane composition and temperature represent two fundamental parameters for the achievement of the desired insulin delivery rate. In particular, insulin permeation through poly(hydroxyethylmethacrylate) increases with an increase in temperature. On the contrary, insulin permeation through poly(N-acryloylpyrrolidine) copolymers increases with a decrease in temperature.

Interestingly, membrane permeability can be modified by the application of an electric field. Indeed, electrophoretic migration of a charged macrosolute within a hydrated membrane depends on the effect of electrical forces acting on the solute and its counterions in the adjacent electrolyte solution [29]. It is well known that [30] four distinct electrochemical and electromechanical mechanisms concur in determining transport of proteins and neutral solutes across hydrogel membranes: (1) electrically and chemically induced swelling of a membrane to alter the effective pore size and permeability, (2) electrophoretic augmentation of solute flux within a membrane, (3) electroosmotic augmentation of solute flux within the membrane, and (4) electrostatic partitioning of charged solutes into charged membranes. In other words, the application of an electric field can result in control of solute flux by a combination of the electrophoretic and electroosmotic mechanisms. Pasechnik and coworkers [31] report an increase in the effective pore radius of ultrafiltration membranes due to electrodynamic effects.

Burgmeyer and Murray [32] observe changes in the ionic permeability of polypyrrole redox membranes using a voltage-controlled electrochemical reaction. Eisenberg and Godzinsky [33] can modify the restricted diffusion of sucrose through collagen membranes via electrodiffusion (this is due to the effect of the electric field on concentration profiles within the membrane), obtaining flux changes up to 25%. Nussbaum and Godzinsky [34] obtain reversible changes in the uniaxial swelling of poly(methylmethacrylate) (PMMA) membranes via electrodiffusion control of intramembrane ionic strength. Application of an electric field across a hydrated polyelectrolyte membrane, such as PMMA, yields a net force on the space charge in the fluid phase, which contains an excess of counterions over cations. This force, transferred to the solvent, results in an electroosmotic fluid flow relative to the solid membrane. Godzinsky and Grimshaw [29] observe a volume flux of $1.2 \times 10^{-6}$ m/s at the direction of the current across a 3.1 cm² PMMA membranes, fixing pH = 7 and current density equal to 320 A/cm². As soon as the current is cut off, the flow is stopped.

Mathiowitz [35–40] realizes reservoir-type delivery systems recurring to a photochemical control. Microcapsules, built up by interfacial polymerization of polyamide, also contain azobisisobutyronitrile, a substance that emanates nitrogen due to a photochemical action. Accordingly, after exposition to light, microcapsules’ internal pressure increases (as a result of nitrogen release) until membrane rupture and consequent contents release.

Self-regulated delivery systems [41] are closed-loop controlled devices in which the release is modulated by the system, in response to feedback information, excluding any external intervention. For example, it is possible to use pH as an environmental stimulus to deliver a drug in a desired gastrointestinal (GI) zone. Basically, the polymeric membrane ruling drug release rate from the delivery system can be poorly swollen and, thus, scarcely permeable with respect to drug, at a low pH (typical of stomach). On the contrary, if it shows a considerable swelling degree at higher pH, it allows drug release in the intestine where pH is considerably increased. A typical example of self-regulated delivery system using membranes concerns insulin delivery. Some authors suggest the immobilization of glucose oxidase in pH-responsive polymeric hydrogel membranes surrounding a saturated insulin solution (Figure 15.1). As soon as glucose penetrates inside the membrane, glucose oxidase catalyzes its conversion to gluconic acid. Consequently, pH lowering in the membrane microenvironment takes place. This pH decrease, determining membrane swelling, greatly improves permeability toward insulin that is copiously released. Horbett and coworkers [42], for example, use N,N-dimethylaminoethyl methacrylate (DMA), hydroxymethylmethacrylate (HEMA), and tetraethylene glycol dimethacrylate (TEGDMA). Membranes are prepared at −70°C by radiation polymerization in order to preserve enzymatic activity. To get a sufficient insulin permeability, HEMA–DMA polymerization is started in order to have a two-phase membrane: the continuous one is the polymer-rich phase, while the dispersed one contains solvent and unreacted monomers. When gelation occurs after the phase separation, the dispersed phase is fixed in the space to form of porous structure. Typically, pore diameter ranges between 1 and 10 µm [43], and the addition of glucose provokes an insulin permeability increase equal to 2.4–5.5 times. Ishihara [44], following a similar approach, uses 2-hydroxyethylacrylate (HEA)-N,N-dimethylaminoethylmethacrylate (DMA), 4-trimethylsilystyrene (TMS), by radical polymerization of the corresponding monomers in DMF. The mole fractions of HEA, DMA, and TMS in the copolymer are 0.6, 0.2, and 0.2, respectively. Membranes are prepared by
solvent casting. Capsules containing insulin and glucose oxidase are prepared by an interfacial precipitation method using gelatin as an emulsion stabilizer. The average diameter of the polymer capsules obtained was 1.5 mm.

Iwata and coworkers [45] pretreat porous poly(vinylidene fluoride) (PVDF) membranes (average pore size of 0.22 µm) by air plasma, and subsequently, acrylamide (AAm) is graft polymerized on the treated surface. The polyacrylamide is then hydrolyzed to poly(acrylic acid) (PAA). In the pH range of 5–7, grafted PAA chains are solvated and dissolved, but cannot diffuse into the solution phase because of grafting to the porous membrane. Accordingly, membrane pores are effectively closed. In the pH range of 1–5, the chains collapse and the permeability increases. To achieve the sensitivity of the system toward glucose, glucose oxidase was immobilized onto a poly(2-hydroxyethylmethacrylate) gel.

Siegel and coworkers [46] approach insulin delivery by means of an implantable mechanochemical pump converting changes in blood glucose concentration into a mechanical force pumping insulin out of the device. Briefly, this device is made up by three chambers (Figure 15.2). Chamber I contains an insulin solution, chamber II contains aqueous fluid, while chamber III is made up by a pH-sensitive polymer membrane that expands upon glucose concentration increases. Chamber I is separated from the environment by a one-way valve opening when pressure in the pump exceeds that of the environment. Chamber II communicates with body fluids through a one-way valve opening when the pressure inside the pump is less than that of the external medium. Hydrogel (chamber III) is maintained in contact with the surrounding environment via a rigid membrane permeable only to small molecules and impermeable to large molecules such as plasma proteins. Chambers II and III are separated by an elastomeric diaphragm, while chambers I and II are separated by a movable partition.

Of course, insulin release is not the unique target in the delivery field. Indeed, for example, Ishihara and coworkers [47] match the problem of urea release using a non-erodible membrane. The system is constituted by a pH-sensitive membrane (copolymerization of 4-carboxyacrylanilide and methacrylate) sandwiched among a membrane containing urease immobilized in free radically cross-linked


FIGURE 15.2 Mechanochemical insulin pump. (a) No glucose excess in the blood, (b) glucose excess: insulin delivery, and (c) stop to insulin delivery due to glucose concentration decrease. (From Kost, J. and Langer, R., Adv. Drug Deliv. Rev., 46, 125, 2001. With permission.)
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15.2 MASS TRANSPORT

15.2.1 FACTORS AFFECTING DRUG PERMEATION

As most of the membranes used to modulate drug release kinetics are made up by polymers, this section focuses the attention on the typical mechanisms ruling mass transport through a polymeric network (whose structure has been previously described). At this purpose, it is necessary to firstly define the concept of membrane porosity as polymeric network can be classified as macroporous, microporous, and nonporous systems [49]. In the first two categories, drug diffusion occurs essentially through pores. For macroporous systems, pores range between 0.1 and 1 μm, which are much larger than diffusant molecule size. For microporous systems, pore size ranges between 0.005 and 0.02 μm, which means, approximately, slightly larger than diffusant molecule size. Finally, nonporous systems have no pores, and the molecules diffuse through network meshes. In this case, consequently, only the polymeric phase exists and no pore phase is present. While for macro- and microporous networks drug diffusion is mainly affected by pore topology, for nonporous structures, polymer swelling, polymer erosion, network topology, and drug/polymer interaction play the key role in determining drug diffusion. Indeed, it may happen that upon contact with the release environment, polymeric network undergoes a swelling process, this being particularly important in the case of a dry membrane. This implies a molecular rearrangement of polymeric chains that tend to reach a new equilibrium condition as the old one was altered by the presence of the incoming external solvent [50]. The time required for this rearrangement depends on the relaxation time \( t_r \) of the given polymer/solvent system, which, in turn, is a function of both solvent concentration and temperature. If \( t_r \) is much lower than the characteristic time of diffusion \( t_d \) of the solvent (defined as the ratio of the square root of a characteristic length and the solvent diffusion coefficient at equilibrium), then solvent adsorption may be described by means of Fick’s law with a concentration-dependent diffusion coefficient. On the contrary, if \( t_r \) is much greater than \( t_d \), then a Fickian solvent adsorption with constant diffusivity takes place. Despite this complex phenomenology, however, in both cases, the diffusion of drug molecules crossing the membrane may be described by Fick’s law with a nonconstant diffusion coefficient (this is due to the variations of network meshes), and the macroscopic drug kinetics is defined as Fickian. When \( t_r \approx t_d \), solvent adsorption does not follow Fick’s law of diffusion [51–53], and consequently, also the diffusion of drug molecules crossing the membrane is not Fickian [54,55]. Accordingly, solvent absorption and drug permeation depend also on the polymer/solvent couple viscoelastic properties [56].

Polymer erosion can take place because of chemical and physical reasons. Under particular physiological conditions, the hydrolysis of eventually present water-labile bonds incorporated in the polymer can cause chain breaking. Moreover, erosion can be also due to enzyme attack and chemical reactions on particular polymeric chain sites [49]. On the contrary, in physically cross-linked matrices, erosion is due to chain disentanglement, induced by the matrix swelling fluid and the hydrodynamic conditions imposed in the release environment. Obviously, polymer characteristics play a very important role in erosion kinetics as extensively documented by the review of Miller-Chou and coworkers [57]. Erosion can be of two different types [49,58]: (1) surface or heterogeneous erosion and (2) bulk or homogeneous erosion. While in the first case only the outer parts of the matrix are affected by erosion, in the second case, the phenomenon also affects the polymeric bulk phase. Homogeneous erosion is usually due to a rapid swelling fluid uptake by the matrix system and consequent polymeric network degradation due to chemical reasons as discussed earlier. On the contrary, surface erosion can be caused by both chemical (in this case, the swelling fluid uptake is slower) and physical reasons, namely, hydrodynamic conditions imposed in the release environment. On the basis of the relative chain cleavage and solvent diffusion rate, a system can be defined surface eroding or bulk eroding. In particular, if solvent diffusion is much slower than polymer degradation, we are dealing with a surface-eroding system. Surface erosion, also referred to as polymer dissolution in case of physically cross-linked matrices, can be further subdivided into two categories on the basis of the amorphous or semicrystalline nature of the polymer. Indeed, while in the case of amorphous polymers only chain disentanglement is necessary for erosion, in the case of semicrystalline polymers, crystal unfolding precedes chain disentanglement, thus resulting in slower erosion kinetics [59].

Polymeric network topology heavily reflects on drug diffusion as it concurs in determining the drug diffusion coefficient as later on discussed. Additionally, polymeric network can also be responsible for a non-Fickian diffusion. Indeed, in the presence of a very complex topology,
deriving from a high internal disorder degree, the network can assume fractal characteristics [60]. If wide network meshes are defined as accessible sites for the diffusing drug and small network meshes (beside, obviously, polymeric chains) as forbidden sites, the entire network can be seen as a percolative network (fractal network), if forbidden sites approach a threshold value [61,62]. It is well known that diffusion on percolative (fractal) networks differs a lot from diffusion in nonfractal networks and release kinetics is different [60,63].

Although drug–polymer interactions can be expected to take place in several cases [64,65], particular importance is assumed by electrostatic interactions as reported by Singh and coworkers [66,67]. According to these authors, drug binding on polymeric chains follows a Langmuir isotherm mechanism characterized by an adsorption and desorption rates depending on drug-free and bound concentration and on adsorption and desorption constants. Consequently, drug permeation through the membrane is the result of two phenomena, namely, diffusion and adsorption—desorption.

### 15.2.2 Continuity Equation

In the case of diffusion of a substance through a stationary solid or semisolid phase such as the polymeric network of a membrane, it is convenient to view the stationary phase as a fixed reference and to consider only the flux of mobile components relative to the stationary phase. Mass conservation law reads as follows [68]:

$$\frac{\partial C_i}{\partial t} = \nabla \cdot F_i + R_i$$  \hspace{1cm} (15.1)

where $C_i$ and $F_i$ are, respectively, the $i$th species concentration (mass/volume) and flux (mass/surface time)

$t$ is time

$R_i$ is the $i$th component generation rate (mass/volume time)

while the scalar product between the operator nabla ($\nabla$) and $F_i$, in a Cartesian coordinate system (for the $i$th component generation rate (mass/volume time) respective, the $i$th species diffusion coefficient. Accordingly,

$$F_i = -D_{ix} \frac{\partial C_i}{\partial x}$$

$D_{ix}$ is the $i$th species diffusion coefficient. Accordingly,

in a Cartesian coordinate system, $F_i$ components read as follows:

$$F_i = -D_{ix} \frac{\partial C_i}{\partial x}, \quad F_y = -D_{iy} \frac{\partial C_i}{\partial y}, \quad F_z = -D_{iz} \frac{\partial C_i}{\partial z}$$  \hspace{1cm} (15.4)

As discussed in Section 15.2.1, it may happen that Equation 15.3 does not hold because of polymeric chain relaxation phenomena occurring during diffusion. In this case, indeed, the hypothesis of an instantaneous proportionality between $F_i$ and $\nabla C_i$ does not work, and a time dependence has to be considered. Several approaches have been proposed to interpret this aspect. For instance, Joshi and Astarita assume a time-dependent composition at the polymer/penetrant interface [69]. In an interesting series of papers, Cohen firstly generalized Crank’s idea [54] of a time-dependent diffusion coefficient [70], and then supposed that flux can be properly described by coupling the concentration and stress gradients, being the stress dependent on concentration and time via a Maxwell-like viscoelastic relationship [71]. Later on, Cohen and coworkers developed and improved the aforementioned approach by modifying the stress dependence on time and concentration [72–74].

The existence of a stress-related convective contribution to flux is postulated by Frisch and coworkers [75] and taken into consideration also by other authors [76,77]. According to Adib and Neogi [78] and Camera-Roda and Sarti [79], the flux may depend on the history of the concentration gradient. The most general theory about diffusion in a viscoelastic polymer matrix was developed by Lustig and coworkers [80] since they assume that the flux depends on several driving forces such as temperature gradient, species’ inertial and body forces, chemical potentials, and stress gradient. A good compromise between simplicity and theoretical correctness is given by the approach of Camera-Roda and Sarti [81]. Basically, they assume that $F_i$ may be expressed as the sum of two terms: $F_{i\rho}$ characterized by a zero relaxation time and representing the Fickian contribution to the global flux, and $F_{i\rho}$, characterized by a nonzero relaxation time and representing the non-Fickian contribution to the global flux.

Accordingly, $F_i$ can be expressed as

$$F_i = F_{i\rho} + F_{i\rho}$$

$$F_{i\rho} = -D_{i\rho} \nabla C_i, \quad F_{i\rho} = -D_{i\rho} \nabla C_i - \tau \frac{\partial F_{i\rho}}{\partial t}$$  \hspace{1cm} (15.5)

where

$\tau$ is the relaxation time of the given polymer/diffusing molecule system

$D_{i\rho}$ is the diffusion coefficient relative to the Fickian flux, while $D_{i\rho}$ is the diffusion coefficient relative to the non-Fickian flux

In this approach, the time dependence is considered in the relaxation flux $F_{i\rho}$. It is worthwhile to note that Equation 15.5
corresponds to considering \( F_\alpha(t + \tau) = F_\alpha \). In fact, by developing this equation in Taylor series in the neighborhood of \( t \), Equation 15.5 is obtained. This reflects the memory of the non-Fickian flux.

Grassi and coworkers [50] improved the Camera-Roda and Sarti model assuming that \( F_\alpha \) is the sum of different contributions, each one characterized by its proper relaxation time. In this manner, the description of membrane viscoelastic properties is more adherent to reality.

While the time-dependent approach applies to describe possible membrane swelling (or deswelling) due to the presence of the external release environment fluid, it is not necessary in the case of drug permeation through a swollen membrane. The same is true when membrane swelling (or deswelling) is very fast or very slow in comparison to the duration of drug permeation through the membrane. A fast membrane swelling (or deswelling) will only reflect on a rapid drug diffusion coefficient variation.

### 15.2.3 Diffusion Coefficient

Once an appropriate frame of reference is chosen, a two-component system \((A, B)\) may be described in terms of the mutual diffusion coefficient (diffusivity of \( A \) in \( B \) and vice versa). Unfortunately, however, unless \( A \) and \( B \) molecules are identical in mass and size, mobility of \( A \) molecules is different with respect to that of \( B \) molecules. Accordingly, the hydrostatic pressure generated by this fact will be compensated by a bulk flow (convective contribution to species transport) of \( A \) and \( B \) together, that is, of the whole solution. Consequently, the mutual diffusion coefficient is the combined result of the bulk flow and the molecules’ random motion. For this reason, an intrinsic diffusion coefficient \((D_A\) and \( D_B\)) accounting only for molecules’ random motion, has been defined. Finally, by using a radioactively labeled molecules, it is possible to observe the rate of diffusion of one component (let’s say \( A \)) in a two-component system, of uniform chemical composition, made up by labeled and not labeled \( A \) molecules. In this manner, the self-diffusion coefficient \((D_A^*=)\) can be defined [54]. Interestingly, it can be demonstrated that both \( D_A \) and \( D_B^*\) are concentration dependent. Indeed, the force \( f \) acting on an \( A \) molecule at point \( X \) is [1]

\[
f = -\nabla \mu_A
\]

(15.6)

where \( \nabla \mu_A \) is the \( A \) chemical potential gradient. Accordingly, the total force \( f_T \) acting on all molecules is

\[
f_T = -C_A \nabla \mu_A
\]

(15.7)

where \( C_A \) is concentration. The assumption that the flux \( F_A \) is proportional to the total force yields to

\[
F_A = \frac{C_A}{\sigma_A \eta} \nabla \mu_A
\]

(15.8)

where \( \sigma_A \eta \) is a resistance coefficient connected with diffusing molecule mobility [1,54] Remembering the definition of chemical potential [82]

\[
d\mu_A = RT d(\ln(a_A))
\]

(15.9)

where

- \( a_A \) is the activity
- \( R \) is the universal gas constant
- \( T \) is temperature, it follows

\[
F_A = \frac{RT}{\sigma_A \eta} \frac{d(\ln(a_A))}{d(\ln(C_A))} \nabla C_A
\]

(15.10)

Accordingly, \( D_A \) can be expressed by

\[
D_A = \frac{RT}{\sigma_A \eta} \frac{d(\ln(a_A))}{d(\ln(C_A))}
\]

(15.11)

Repeating the same treatment for \( D_A^* \) and remembering that in this case concentration and activity coincide due to obvious solution ideality, it follows that

\[
D_A^* = \frac{RT}{\sigma_A \eta}
\]

(15.12)

Assuming that \( \sigma_A \eta = \sigma_B \eta \), it descends that

\[
D_A = D_A^* \frac{d(\ln(a_A))}{d(\ln(C_A))}
\]

(15.13)

In conclusion, thus, the drug diffusion coefficient in a solvent is both concentration and temperature dependent. In the case of drug transport through swollen nonporous membranes, the physical frame is complicated by the presence of polymeric chains. Assuming that only drug molecules are moving due to a chemical potential gradient (in this sense, polymeric chains and the swelling agent molecules are retained immobile), the drug diffusion coefficient will be mainly affected by the presence of polymeric chains. Indeed, polymer chains have been proposed to retard solute movement by reducing the average free volume per molecule available to the solute, by increasing the hydrodynamic drag experienced by the solute, and by acting as physical obstructions, thereby increasing the path length of the solute [83]. Basically, drug diffusion estimation can be performed recurring to the free volume theory, the hydrodynamic theory, and the obstruction theory [83]. Free volume theory [84] assumes that solute diffusion in a liquid is due to solute jumping into voids formed in the liquid space due to liquid molecules’ thermal motion. Solute diffusion is dependent on the jumping distance, the thermal velocity of the solute, and the probability that there is a hole free volume adjacent to the molecule. If, in addition, the presence of a polymeric network is considered, this
Hydrodynamic theory [68], based on Stokes–Einstein equation, postulates that solute is represented by a very large sphere in comparison with the surrounding small liquid-phase molecules. Solute mobility, and thus its diffusion coefficient, depends on the frictional drag exerted by liquid-phase molecules. For heterogeneous gels (rigid polymeric chains), the author proposes

$$\frac{D_s}{D_0} = \exp\left(-\frac{3\pi LN_A}{M_f \ln(L_c/2r_s)} r_s^{1/2}\right)$$  \hspace{1cm} (15.15)$$

where

- $L_s$ and $M_s$ are, respectively, the polymer chain’s length and molecular weight
- $N_A$ is Avogadro’s number
- $r_s$ is the polymer fiber radius

For homogeneous gels (flexible polymeric chains), the same author proposes

$$\frac{D_s}{D_0} = \exp\left(-k_c r_s^{0.75}\right)$$  \hspace{1cm} (15.16)$$

where $k_c$ is a parameter depending on the polymer solvent system.

Models based on obstruction theory assume that the presence of impenetrable polymer chains causes an increase in the path length for diffusive transport. The polymer chains act as a sieve, allowing passage of a solute molecule only if it can pass between the polymer chains. Mackie and Meares [87], assuming solute molecule of the same size as polymer segments and assuming that solute transport occurs only within the free sites, suggest

$$\frac{D_s}{D_0} = \left(\frac{1 - \varphi}{1 + \varphi}\right)^2$$  \hspace{1cm} (15.17)$$

On the basis of more refined speculations, Ogston and coworkers [88] propose

$$\frac{D_s}{D_0} = \exp\left(-\frac{r_s + r_p}{r_s} \varphi^{1/2}\right)$$  \hspace{1cm} (15.18)$$

According to Amsden [83], hydrodynamic approach should be used to deal with homogeneous hydrogels, while, for heterogeneous hydrogels, obstruction is more consistent with experimental data.

In the case of porous membranes, where solute diffusion takes place inside the liquid filling the pores, it is usual defining an effective diffusion coefficient $D_e$:

$$D_e = \frac{D_s \varepsilon}{\tau}$$  \hspace{1cm} (15.19)$$

where

- $\varepsilon$ is the matrix void fraction (porosity)
- $\tau$ is tortuosity
- $D_s$ is solute diffusion coefficient in the liquid filling the pores [89]

It is sometimes desirable [90] to incorporate into this expression a partition coefficient, $K_p$, for possible solute adsorption on pore walls and a restriction coefficient, $K_r$, accounting for hindered diffusion and defined by

$$K_r = (1-\lambda)^2, \quad \lambda = \frac{r_s}{r_p}$$  \hspace{1cm} (15.20)$$

where $r_p$ is pore radius. Accordingly, Equation 15.19 becomes

$$D_e = D_s \frac{\varepsilon}{\tau} K_p K_r$$  \hspace{1cm} (15.21)$$

15.2.4 MODELING EXAMPLES: SWELLABLE AND NONSwellable MEMBRANES

Drug diffusion through a nonswellable/deswellable/erodible (or through an already swollen) membrane can be described by means of Fick’s law. Indeed, assuming that drug concentration on one side of the membrane (donor environment) is always constant and equal to $C_0$, that drug concentration $C_1$ on the other side (receiver environment) never sensibly detaches from zero (sink conditions), that drug diffusion takes place only in one dimension ($X$), that membrane thickness is constant, that drug diffusion coefficient $D_0$ inside the membrane is constant, and that no mass transport resistance exists in the membrane/donor and membrane/receiver interface (this means that, e.g., we assume a negligible effect of the unavoidable presence of...
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Equations 15.5 and 15.24 through 15.26 have to be numerically solved [93] with the following initial conditions:

\[ J = 0, \quad C = 0, \quad -\frac{L_{in}}{2} \leq X \leq \frac{L_{in}}{2} \]  \hspace{1cm} (15.27)

and boundary conditions:

\[ C = C_{eq}, \quad X = \pm \frac{L_b}{2} \]  \hspace{1cm} (15.28)

where \( L_{in} \) is the initial membrane thickness, while \( L_b \) is the position of the swelling membrane contours. Of course, membrane thickness can be calculated supposing that its volume is given by the arithmetic addition of solvent and polymer volume. Assuming that the most important effect of matrix swelling/shrinking is to modify the solute diffusion coefficient \( D_x \) (and the Peppas–Reinhart equation (15.14) can be considered to account for this), permeation can be described by the continuity equation (Equation 15.1) where the generative term \( R_i \) is set to zero and the following initial and boundary conditions hold:

**Initial conditions**

\[ C_d = 0, \quad \frac{L_{in}}{2} < X < \frac{L_{in}}{2} \]  \hspace{1cm} (15.29)

**Boundary conditions**

\[ C_d = 0, \quad X = \frac{L_b}{2} \]  \hspace{1cm} (15.30)

\[ C_d = C_i, \quad X = -\frac{L_b}{2} \]  \hspace{1cm} (15.31)

While \( C_d \) and \( C_i \) are, respectively, solute concentration and solubility, Equation 15.29 implies that the membrane is solute-free at the beginning, Equation 15.30 accounts for sink conditions in the receiver, and Equation 15.31 states that solute concentration in the donor is always constant and equal to solubility. Figure 15.3 shows the comparison between model best fitting (solid line) and experimental data relative to hydrocortisone permeation through a copolymer made up of poly(N,N-dimethylaminoethyl methacrylate) (DMAEMA) and AAm (molar ratio: 57% DMAEMA, 33% AAm). As this copolymer undergoes a sharp deswelling passing from 20°C to 40°C, hydrocortisone permeation is considerably decreased when temperature is risen to 40°C. Model best fitting reveals that hydrocortisone diffusion coefficient in the DMAEMA-AAm copolymer at 40°C is 1/10 of that at 20°C.
15.2.5 Osmotic Systems

Osmosis is the natural movement of a solvent through a semi-permeable membrane into a solution of higher solute concentration, leading to equal solute concentrations on both sides of the membrane [94]. A semipermeable membrane can be crossed by solvent molecules, but solute (ionic or high-molecular-weight compounds) permeation is impeded. Solvent migration from one side of the membrane to the opposite one takes place in order to render equal solute and solvent chemical potentials across the membrane. Osmotic pressure $\pi$ can be expressed by

$$\pi = \frac{\mu_L - \mu_R}{\nu}, \quad \pi = -\frac{RT}{\nu} \ln(a) \quad (15.32)$$

where
- $\nu$ is solvent partial molar volume
- $\mu_L$ is solute chemical potential on the left of the membrane (initially solute-free environment)
- $\mu_R$ is solute chemical potential on the right of the membrane
- $a$ is the solvent activity on the membrane right side environment

When hydrostatic pressure in the right environment (initial solute richer environment) equals the osmotic pressure $\pi$, the net solvent flux ends. According to nonequilibrium thermodynamics, the rate of solvent transport $dV/dt$ through the membrane is given by [95]

$$\frac{dV}{dt} = \frac{A}{h} L_P (\sigma \Delta \pi - \Delta P) \quad (15.33)$$

where
- $A$ is the cross-sectional area for transport
- $h$ and $L_P$ are, respectively, membrane thickness and hydraulic permeability
- $\sigma$ is the reflection coefficient
- $\Delta \pi$ and $\Delta P$ are the osmotic and hydrostatic pressure differences across the membrane

As, typically, $\Delta P \ll \Delta \pi$, Equation 15.33 simplifies into

$$\frac{dV}{dt} = \frac{A}{h} k \Delta \pi, \quad k = L_P \sigma \quad (15.34)$$

where $k$ can be taken as the effective membrane permeability. Equation 15.34 is the basic equation for the calculation of the amount $m$ of drug released from an osmotic pump. Indeed, since in an osmotic pump the volume of drug solution pumped out is equal to that ($V$) of external solvent entered in the pump through the semipermeable membrane, the rate of drug released will be

$$\frac{dm}{dt} = \frac{dV}{dt} c = \frac{A}{h} k \Delta \pi c \quad (15.35)$$

where $c$ is the drug concentration of the solution contained in the osmotic pump housing.

15.2.6 Electrotransport

In order to improve drug permeation through the skin, recourse to an electrical field can be made. The electrically assisted delivery systems are based on this idea. Typically, electrotransport is due to iontophoresis, electroosmosis, and electroporation [96]. Iontophoresis consists of the use of an electric current to drive charged drug molecules into the skin by placing them under an electrode of like charge. Accordingly, a positively charged drug should be placed under the anode, or positive electrode, and the resulting electric repulsion would provide the driving force for drug permeation through the skin. Typically, a 0.5 mA/cm$^2$ current is used (this intensity being unable to cause skin damages) even if drug permeation can be modulated by acting on current intensity. Electroosmosis is the phenomenon according to which a bulk fluid flow rises when a charged porous membrane is subjected to a voltage difference. This fluid flow can be up to microliters per hour per square centimeters of hairless mouse skin [97]. Since the skin is a perm-selective membrane with negative charge at physiological pH, the electroosmotic flow occurs from anode to cathode, thus increasing the flux of positively charged drugs. Unlike iontophoresis
adopting a continuous low current, electroporation requires the use of high-voltage pulse for a very short duration to render the skin permeable. Probably, electroporation promotes the formation of new aqueous pathways (open for some microseconds and then closed for a time period ranging from milliseconds to hours) that allow the entry of drug molecules by diffusion and local electrophoresis and/or electromosmosis.

For iontophoresis, the flux $F_i$ of an ionic species, $i$, is defined by the Nernst–Planck equation:

$$F_i = -D_i \nabla C_i - z_i m_i f_i C_i \nabla E - C_i V$$

(15.36)

where the first right-hand-side term accounts for Fickian diffusion, while the second is relative to electrical field $E$ effect, and the third represents the electroosmotic flow. In particular, $z_i$ is the ionic species valence, $m_i$ is the mobility, $f_i$ is the Faraday constant, and $V$ is the velocity of the convective electroosmotic flow. In order to get drug profile concentration, we have to solve the continuity equation (Equation 15.1), provided that Equation 15.36 is considered for the flux expression $F_i$ and the generative term $R_i$ is set equal to zero as done by Simon [98].

### 15.3 Membranes: Useful Device for Drug Diffusion Coefficient Measurement

In order to design a controlled release system based on membranes, it is of paramount importance to know the membrane drug diffusion coefficient $D$ [99]. Thus, the measure of $D$ plays a very important role, and the necessity of developing proper models able to interpret the experimental data arises. Several methods are available in literature for the experimental determination of $D$ [100–102]. Among this plethora, we can mention the category of methods deriving from nuclear magnetic resonance (NMR) and dynamic light scattering (DLS) experiments, those based on holographic relaxation spectroscopy, those founded on the determination of the drug concentration profile such as the sectioning and inverse sectioning method [103], and the methods based on drug concentration gradient under stationary and nonstationary gradient. This section, in particular, focuses on the $D$ determination resorting to the analysis of drug permeation through a swollen membrane. At this purpose, the side-by-side apparatus is considered [104,105]. This device consists (see Figure 15.4) of a donor compartment (volume $V_D = 100$ cm$^3$), containing the drug solution, and a receiver compartment (volume $V_R = 100$ cm$^3$) initially filled with pure solvent. Each compartment is equipped with a constant temperature jacket and a magnetic stirrer housed at the bottom of the cell. The membrane (diffusing area $\approx 10$ cm$^2$) is located in the Teflon adapter connecting the receiver and the donor compartments. Drug concentration increase is measured and recorded by means of a personal computer managing a UV spectrophotometer connected to the receiver environment as indicated in Figure 15.4. In order to prevent bubble formation in the detecting system, a surge chamber is inserted between the spectrophotometer and the peristaltic pump that provides for solution recirculation. A more sophisticated configuration permits the substitution of the recirculating system (peristaltic pump, surge chamber, and so on) with an optical fiber apparatus allowing a direct measurement of drug concentration in the receiver environment. The main advantages of this approach lie in the reduction of the receiver environment perturbation and the attainment of an optimal thermal control of the whole system.

#### 15.3.1 Nonswellable Membrane Modeling: Effect of Stagnant Layers and Drug Dissolution

One of the most important errors affecting the determination of the drug diffusion coefficient resorting to permeation data through a swollen membrane may be due to the presence of two stagnant layers. Indeed, an insufficient stirring of both the donor and receiver environment gives origin to two stagnant layers sandwiching the membrane. Neglecting these two layers means to determine the value of the diffusion coefficient referred to the whole trilaminate (made up by the two stagnant layers and the membrane) instead of that referred to the single membrane. This implies an error depending on the sum of the thickness of the two stagnant layers. Sometimes this error may be not negligible, as the membrane thickness may be not small [106–108].

In order to make the present analysis as general as possible, it is assumed that the donor compartment contains an excess amount of undissolved drug. Indeed, this strategy is usually adopted in the attempt of achieving a constant drug
concentration (in this case, drug solubility) in the receiver compartment. Accordingly, the drug dissolution process needs to be carefully taken into account. Nevertheless, it is assumed that Fick’s law for diffusion holds inside the tri-laminate; this means that the effects of all possible chemical or electrical interactions between drug molecules and polymer chains or solvent molecules are accounted for by a drug partition coefficient (membrane/release environment medium) different from the value of one. Of course, a more detailed analysis should account for drug/polymer interaction by coupling, for instance, the diffusion with a drug adsorption/desorption phenomenon on polymer chains [109,110]. Anyway, the usual way to proceed [1,54,111,112] is to implicitly incorporate the polymer/drug interactions in the drug partition coefficient, this being, in the majority of the situations, more than enough to correctly model a permeation experiment. Furthermore, it is supposed that membrane is completely swollen, which means that the solvent concentration has reached its thermodynamic equilibrium value before starting the permeation experiments [113]. Indeed, membrane swelling may heavily influence the features of the drug permeation as previously discussed. Figure 15.5 schematically shows the physical setup, which all the following considerations will be referred to. Fick’s second law for the first layer, the membrane, and the second layer reads as, respectively,

\[
\frac{\partial C_1}{\partial t} = \frac{\partial}{\partial X}\left(D_1 \frac{\partial C_1}{\partial X}\right) \quad (15.37)
\]

\[
\frac{\partial C_2}{\partial t} = \frac{\partial}{\partial X}\left(D_2 \frac{\partial C_2}{\partial X}\right) \quad (15.38)
\]

\[
\frac{\partial C_3}{\partial t} = \frac{\partial}{\partial X}\left(D_3 \frac{\partial C_3}{\partial X}\right) \quad (15.39)
\]

where

\(X\) is the abscissa

\(t\) is the time

\(C_1, C_2, C_3\) and \(D_1, D_2, D_3\) represent, respectively, drug concentration and diffusion coefficient in the first stagnant layer, in the membrane, and in the second stagnant layer.

The aforementioned equations must be solved with the following boundary conditions:

\[
V_d \frac{dC_d}{dt} = -\frac{dM}{dt} + D_3 \frac{\partial C_1}{\partial X}\bigg|_{X=0} \quad (15.40)
\]

\[
\frac{dM}{dt} = -V_d K_t (C_d - C_a) \quad (15.41)
\]

\[
D_1 \frac{\partial C_1}{\partial X}\bigg|_{X=h_1} = D_2 \frac{\partial C_2}{\partial X}\bigg|_{X=h_1} \quad (15.42)
\]

\[
D_2 \frac{\partial C_2}{\partial X}\bigg|_{X=h_1+h_2} = D_3 \frac{\partial C_3}{\partial X}\bigg|_{X=h_1+h_2} \quad (15.43)
\]

\[
V_r \frac{dC_r}{dt} = -D_3 \frac{\partial C_3}{\partial X}\bigg|_{X=h_1+h_2+h_3} \quad (15.44)
\]

**FIGURE 15.5** Physical setup. A membrane is sandwiched among two layers arising in the donor and receiver compartments due to an insufficient stirring. In the donor volume, a dissolution process may take place. (From Grassi, M. and Colombo, I., *J. Control. Release*, 59, 343, 1999. With permission.)
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\[ C_1(X = 0) = K_{1d} C_d \]  
\[ C_2(X = h_1) = K_{21} C_1(X = h_1) \]  
\[ C_2(X = h_1 + h_2) = K_{23} C_2(X = h_1 + h_2) \]  
\[ C_3(X = h_1 + h_2 + h_3) = K_{3r} C_r \]

and the following initial conditions:

\[ C_d = C_1 = C_{d0}, \quad C_r = C_2 = C_3 = 0, \quad M = M_0 \]  

where

- \( C_d \) and \( V_d \) are, respectively, drug concentration and volume of the donor compartment.
- \( M \) is the time-dependent undissolved (solid) drug amount present in the donor compartment.
- \( S \) is the area available for permeation.
- \( K_r \) is the drug dissolution constant.
- \( C_i \) is the drug solubility.
- \( V_r \) is the receiver compartment volume.
- \( h_1, h_1, \) and \( h_2 \) are, respectively, the thicknesses of the first and second stagnant layers and the membrane.
- \( C_{d0} \) and \( M_0 \) are, respectively, the initial drug concentration and undissolved drug amount in the donor compartment.
- \( K_{1d}, K_{21}, K_{23}, \) and \( K_{3r} \) are partition coefficients defined as follows:

\[ K_{1d} = \frac{C_1(X = 0)}{C_d} = \frac{C_{1e}}{C_{d0}} \]  
\[ K_{21} = \frac{C_2(X = h_1)}{C_1(X = h_1)} = \frac{C_{21}}{C_{1e}} \]  
\[ K_{23} = \frac{C_2(X = h_1 + h_2)}{C_3(X = h_1 + h_2)} = \frac{C_{23}}{C_{21}} \]  
\[ K_{3r} = \frac{C_3(X = h_1 + h_2 + h_3)}{C_r} = \frac{C_{3r}}{C_{3r}} \]

being \( C_{d0}, C_{1e}, C_{1o}, C_{2o}, \) and \( C_{3o} \) the drug concentration in the donor and receiver compartments and the drug concentration in the first layer, in the membrane, and in second layer, respectively, at equilibrium. In this way, partition coefficients, defined by Equations 15.50 through 15.53, are thought concentration independent and, thus, time independent. Equation 15.40 represents the drug mass balance made up on the donor compartment: the first right-hand-side term takes into account the dissolution, while the second represents the matter flux, leaving the donor through the first stagnant layer. Equation 15.41 takes into account the reduction of the solid drug \( M \) as the dissolution goes on. When \( M \)
is zeroed, the first term of the right-hand side of Equation 15.40 vanishes. Equation 15.42 imposes that the matter flux leaving the first stagnant layer is equal to that entering the membrane \((X = h_1)\), while Equation 15.43 imposes the equality of the matter flux leaving the membrane and entering the second stagnant layer \((X = h_1 + h_2)\). Equation 15.44 represents the drug mass balance made up on the receiver compartment: the right-hand-side term is the entering drug flux coming from the second layer. Equations 15.45 through 15.48 indicate the partitioning relation holding at the interface in \( X = 0, (h_1, h_1 + h_2), (h_1 + h_2, h_1 + h_2 + h_3) \). Equation 15.49 sets to zero the drug concentration in the membrane, in the second layer, and in the receiver, while it sets to \( C_{d0} \) the drug concentration in the first stagnant layer and in the donor at the beginning of the permeation. An inspection of the aforementioned set of differential equations makes clear that the simpler situation represented by the absence of undissolved drug present in the donor compartment can be obtained by setting \( M_0 = 0 \).

If drug dissolution takes place from a thin tablet, it is reasonable to assume that \( K_r \) is time independent as dissolution surface is, practically, constant. On the contrary, if we are dealing with the dissolution of a powder, this is no longer true as particle radius and, thus, particle surface (this is the dissolving surface) reduce as dissolution proceeds. Indeed, the dissolution of a solid from a plane and uniform surface may be easily modeled by means of the following equation [114]:

\[ V \frac{dC}{dt} = \frac{D_0 S_p}{h} (C_i - C) \]

where

- \( C, C_i, \) and \( V \) are, respectively, the solute concentration, the solute solubility, and the volume of the dissolution medium.
- \( S_p \) is the area of the solid/liquid interface.
- \( D_0 \) is the solute diffusion coefficient in the dissolution medium.
- \( h \) is the thickness of the boundary layer arising between the solid surface and the dissolution medium.

\( h \) strongly depends on the stirring conditions of the dissolution medium [115,116]. Remembering that \( K_r \) is equal to

\[ K_r = \frac{D_0 S_p}{h V} \]

being \( K_r \) the drug dissolution rate, Equation 15.54 may be recast in the following form:

\[ V \frac{dC}{dt} = K_i (C_i - C)V \]

The right-hand side of Equation 15.56 coincides with the dissolution contribute employed in Equation 15.41.
$S_p$, for a plane and uniform surface, does not change as dissolution develops, we may be sure that $K_t$ is time independent. Unfortunately, this is not the case for a dissolving powder. Indeed, in such hypothesis, the dissolution surface decreases as the time goes on. The starting value of $S_p$, $S_{p0}$, is equal to the powder surface area and, for a monodisperse powder made up by $N_p$, all equal, spherical particles, is given by

$$S_{p0} = N_p4\pi R_0^2$$  \hspace{1cm} (15.57)

being $R_0$, the particle radius.

At time $t$, the particle radius will be decreased to $R$, and as a consequence, $S_p$ will be equal to

$$S_p = N_p4\pi R^2$$  \hspace{1cm} (15.58)

Then, the $K_t$ time dependency will be given by

$$K_t = \frac{K_d}{V}4\pi R^2$$  \hspace{1cm} (15.59)

Equation 15.59 holds in the hypothesis that the whole powder surface is available for dissolution. This is reasonably accomplished when the dissolution medium is highly stirred so that the particles cannot adhere to the vessel walls or each other. Accordingly, the $K_t$ time dependency, given by Equation 15.59, has to be inserted into Equation 15.40, getting

$$V_d \frac{dC_d}{dt} = 4\pi N_p R^2 K_d(C_s - C_d) + D_s \frac{dC_1}{dX} \bigg|_{X=0}$$  \hspace{1cm} (15.60)

This equation has to be coupled with the $R$ time dependency coming out from a mass balance made up on the trilaminate, the donor and receiver compartments. This mass balance reads

$$M = M_0 + V_d(C_{d0} - C_d) - V_i C_i - \int_{h_i}^{h_i + h_2} C_1 S dX - \int_{h_i}^{h_i + h_2} C_2 S dX - \int_{h_i + h_2}^{h_i + h_2 + h_3} C_3 S dX$$  \hspace{1cm} (15.61)

Bearing in mind that

$$M = N_p M_p = N_p \frac{4}{3}\pi R^3$$  \hspace{1cm} (15.62)

it follows

$$R = \left(\frac{3M}{N_p4\pi}\right)^{1/3} = R_0 \left(\frac{M}{M_0}\right)^{1/3}$$  \hspace{1cm} (15.63)

being

$$M_0 = N_p \frac{4}{3}\pi R_0^3$$  \hspace{1cm} (15.64)

where $A$ is the powder surface per unit mass before dissolution. Equation 15.63 is the well-known Hixson–Crowell equation [117]. The effects of the $K_t$ reduction are more evident when the dissolution phenomenon implies a considerable decreasing of the particle radius. Indeed, in this case, the dissolution surface will be strongly reduced, and as a consequence, the dissolving drug mass going into the donor compartment will be decreased. Obviously, the solution of the aforementioned set of equations may be achieved only by means of a numerical method like the control volume method [93], which is an implicit finite difference method suitable to solve such kind of problems.

Interestingly, if the drug concentration profile inside the two stagnant layers and the membrane has always a linear trend, $K_t$ is time independent, and the drug diffusion coefficient is concentration independent (these conditions are usually met for thin membranes and well-stirred donor and receiver compartments), the proposed numerical model has the following analytical solution:

$$C_d(t) = A_1 + A_2e^{m_1t} + A_3e^{m_2t}$$  \hspace{1cm} (15.65)

$$C_r(t) = B_1 + B_2e^{m_1t} + B_3e^{m_2t}$$  \hspace{1cm} (15.66)

$$M(t) = M_0 + E_1(e^{m_1t} - 1) + E_2(e^{m_2t} - 1)$$  \hspace{1cm} (15.67)

where $A_1$, $A_2$, $A_3$, $m_1$, $m_2$, $B_1$, $B_2$, $B_3$, $E_1$, and $E_2$ are defined by the following equations:

$$m_1 = 0.5\left(\frac{-T_2 - G + x_b - Y}{\sqrt{(T_2 - G + x_b - Y)^2 - 4((x_b - Y)(T_2 - G) - T_2 x_0)}}\right)$$  \hspace{1cm} (15.68)

$$m_2 = 0.5\left(\frac{-T_2 - G + x_b - Y}{\sqrt{(T_2 - G + x_b - Y)^2 - 4((x_b - Y)(T_2 - G) - T_2 x_0)}}\right)$$  \hspace{1cm} (15.69)

$$A_1 = -\frac{(x_b - Y)K_tC_t}{m_1 m_2}$$  \hspace{1cm} (15.70)

$$A_2 = \frac{K_tC_t - (x_b - Y)K_tC_t/m_1 - (m_2 - (T_2 - G))C_t}{m_1 - m_2}$$  \hspace{1cm} (15.71)

$$A_3 = \frac{K_tC_t - (x_b - Y)K_tC_t/m_2 - (m_1 - (T_2 - G))C_t}{m_2 - m_1}$$  \hspace{1cm} (15.72)
where  

\[
B_1 = - \frac{K C_s + (T g - G) A_2}{T_z} \\
B_2 = \frac{A_1}{T_z} (m_1 - (T g - G)), \quad B_3 = \frac{A_1}{T_z} (m_1 - (T g - G))
\]

In order to empirically adapt Equations 15.65 through 15.67 for the description of drug permeation through thick membranes, it is convenient to introduce a lag time \( t \), taking in account the time required to get a linear concentration profile in the two stagnant layers and in the membrane. Accordingly, it follows

\[
\frac{1}{\gamma} = \frac{\alpha \gamma}{\alpha - \delta}, \quad \frac{1}{\beta} = \frac{\alpha \gamma}{\alpha - \delta}, \quad \frac{1}{\gamma} = \frac{1}{\gamma} + \frac{1}{\alpha \gamma}
\]

Equations 15.79 and 15.80 can describe the linear part of the permeation curve [118].

### 15.3.2 Examples: Theophylline Permeation through Calcium Alginate Membranes

For its large use in the pharmaceutical field, theophylline monohydrated (\( \text{C}_1\text{H}_8\text{N}_4\text{O}_2 \cdot \text{H}_2\text{O} \); Carlo Erba, Milano) can be used as model drug to measure the permeability of calcium alginate membranes having different thickness. Membranes are prepared by gradually adding the dry polymer powder (Protanal LF 20/60, Na salt of alginic acid; Protan Biopolymer, Drammen, Norway) into a highly stirred thermostatic (40°C) vessel containing demineralized water. In order to eliminate air bubbles produced by stirring, the solution undergoes a further mixing stage under vacuum for 5 min. The solution is put in a Petri dish, which in turn is immersed for 30 min in an aqueous solution containing 0.05 M CaCl\(_2\) and 0.4 M NaCl. CaCl\(_2\) represents the Ca\(^{2+}\) source necessary for the gel formation (based on Ca\(^{2+}\)-mediated egg-box junctions [5,119]), while NaCl is added in order to guarantee a better gel homogeneity as suggested by Skjak-Braek and coworkers [119]. The gel membrane is washed for 2 min in demineralized water in order to remove salts from its surfaces, and then its thickness is determined as the average of four measurements taken into different membrane points by means of an electronic caliper (Mitutojo, type IDC 112MCB, Japan).

The side-by-side apparatus used (see Figure 15.4) is characterized by donor and receiver compartments having equal volumes \( (V_r = V_r = 100 \text{ cm}^3) \) and a surface area \( S \) available for permeation of \(~10 \text{ cm}^2\). While, initially, the donor compartment contains a saturated theophylline solution in presence of not dissolved theophylline, the receiver compartment is initially filled with demineralized water. By means of the surrounding jacket, temperature is kept uniform and constant in the whole system, while a magnetic stirrer (600 rpm) ensures a good mixing in both compartments. The drug concentration increase is measured and recorded by means of a personal computer managing a UV spectrophotometer (271 nm, UV-VIS spectrophotometer, Lambda 6, PerkinElmer, United States) connected to the receiver environment. Permeation experiments, led in duplicate, are performed at 25°C and 37°C and for three different polymer concentrations (%P): 1, 2, and 4 w/w%. In order to get a reliable determination of the theophylline diffusion coefficient, all other model parameters have to be measured in advance [118]. In particular, theophylline water solubility \( C_s (6,681 \pm 42 \mu\text{g/cm}^3 \text{ at } 25^\circ\text{C}; \ 12,495 \pm 104 \mu\text{g/cm}^3 \text{ at } 37^\circ\text{C}) \), its water diffusion coefficient \( D_w (6.1 \pm 0.4) \times 10^{-6} \text{ cm}^2/\text{s} \text{ at } 25^\circ\text{C}; (8.2 \pm 0.6) \times 10^{-6} \text{ cm}^2/\text{s} \text{ at } 37^\circ\text{C}) \), the powder dissolution constant \( K_{id} (1.57 \times 10^{-3} \text{ cm/s} \text{ at } T = 25^\circ\text{C}; 1.52 \times 10^{-3} \text{ cm/s} \text{ at } T = 37^\circ\text{C}) \), the partition coefficient \( K_{id} \) between the membrane (calcium alginate gel) and the donor–receiver fluid (water), and finally, the thickness \( h_1 \) and \( h_2 \) of the two stagnant layers (see Table 15.1) are determined. Figure 15.6 shows the trend of the receiver drug concentration \( C_r \) versus time \( t \) for the test performed at 25°C at three different %P (test no. 2, 3, 5). The difference between the curves obtained from tests 2 and 3 are mainly due to different values of \( D_{id} \) since membrane thickness is comparable (see Tables 15.1 and 15.2), while in the case of test 5, membrane thickness is the key parameter governing the difference. Moreover, the nonlinear trend in the beginning part of the curves, regardless of the %P value, indicates that the membranes under consideration cannot be defined as thin. Depending on the %P considered, after a sufficiently long time, the permeation curves assume an almost linear trend indicating that, correspondingly, a linear drug concentration profile is attained inside the trilaminate (two stagnant layers and membrane). Similar considerations can be done for Figure 15.6 where the \( C_r - t \) trend refers to \( T = 37^\circ\text{C} \). Alginites do not give origin to thermosensitive hydrogels, and hence, an increase in temperature does not lead to appreciable changes in the membrane structure, whereas the theophylline diffusion coefficient increases with temperature.
Accordingly, the permeation kinetics is improved at 37°C and \( C_r \) increases more rapidly than at 25°C. An inspection of Table 15.2 reveals that the theophylline diffusion coefficient \( D_2 \) does not sensibly vary with \( \%P \), regardless of the temperature. This can be explained with the fact that the \( \%P \) increase, in the 1%–4% range, does not substantially reflect in an increase of the polymeric network cross-link density, responsible for a reduction of the network mesh size, but it reflects in a higher membrane thickness. Nevertheless, it cannot be also excluded that, due to reduced theophylline dimension (\( \approx 3.8 \, \text{Å} \)) [118,120], polymeric network meshes are always very large even in the case \( \%P = 4 \). Obviously, this result cannot exclude that for higher polymer concentration, typical of some polymeric pharmaceutical membranes, \( \%P \) increase does not reflect in a reasonable, cross-link density increase.

Finally, it is interesting to note that the results obtained by fitting Equations 15.79 and 15.80 (being \( t_r \) and \( D_2 \) the only fitting parameters) on experimental data are, practically, equal to those deducible by fitting the numerical model to the same data (see Table 15.2). Figure 15.7 shows the good agreement between experimental data (open circles) and model best fitting (thick solid line, numerical model; thin solid line, Equations 15.79 and 15.80).

### 15.4 ORAL DELIVERY SYSTEMS

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and, most importantly, patient compliance [121]. In addition, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. Orally delivered pharmacologically active compounds must have favorable absorption and clearance properties and satisfactory metabolic stability to provide adequate systemic exposure to elicit a pharmacodynamic response. If the compounds possess reasonable physicochemical properties and have low to intermediate clearance and reasonable absorption, adequate oral bioavailability may be achieved [122]. Indeed, oral bioavailability, defined as the rate and extent to which the active drug is absorbed from a pharmaceutical form and becomes available at the site of drug action [123], is influenced by several factors including solubility, permeability, intestinal and liver metabolism, rapid biliary, and other efflux pump-mediated excretion and conditions in the GI milieu [124,125]. Thus, both absorption

### Table 15.1

<table>
<thead>
<tr>
<th>T (°C)</th>
<th>No.</th>
<th>( %P )</th>
<th>( K_m ) ( \times 10^4 ) (cm)</th>
<th>( h_m ) ( \times 10^4 ) (cm)</th>
<th>( A ) (cm²)</th>
<th>( h_{ss} ) ( \times 10^4 ) (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>1</td>
<td>1</td>
<td>0.92 ± 0.02</td>
<td>475</td>
<td>10.8</td>
<td>54.8</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>0.83 ± 0.04</td>
<td>450</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>4</td>
<td>0.88 ± 0.01</td>
<td>870</td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>7</td>
<td>1</td>
<td>0.83 ± 0.04</td>
<td>280</td>
<td>10.8</td>
<td>60.7</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>2</td>
<td>0.79 ± 0.001</td>
<td>490</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>4</td>
<td>0.84 ± 0.01</td>
<td>720</td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
<td></td>
<td>655</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


\( T \) is the temperature and \( \%P \) is the polymer percentage in the membrane.
Membranes in Drug Delivery

and elimination processes determine the oral bioavailability $F$ of a given drug. Accordingly, $F$ can be estimated as

$$F = F_a \cdot F_g \cdot F_h \cdot F_l$$  (15.81)

where $F_a$ is the fraction absorbed across the intestinal wall, while $F_g$, $F_h$, $F_l$ are, respectively, the fractions escaping clearance by the GI tract, liver, and lung. The product of fraction available after gut and liver extraction ($F_g \cdot F_h$) following oral administration primarily determines the oral clearance of the drug, although the contribution of lung clearance should also be considered [126]. It is therefore clear that, due to the complexity of drug absorption, the designing of drug release kinetics is of paramount importance and membranes can play an important role in oral delivery systems that are diffusion and dissolution controlled, as well as in ion-exchange resins and osmotic systems. Indeed, apart from the simple taste-masking aim (but this aspect becomes very important when dealing, e.g., with delivery systems devoted to pediatric applications), typically, membranes are used in oral delivery systems to modulate release kinetics by controlling drug diffusion in the release environment or by controlling external solvent penetration in the delivery system. Additionally, membrane can be designed to dissolve in particular physiological conditions in order to ensure drug release in the stomach rather in the intestine or vice versa depending on the drug absorption window. For example, verapamil (calcium channel blocker, indicated as a treatment for hypertension), a water-soluble compound that does not show bioavailability problems, can be administered by means of both reservoir systems (Verelan capsules, Elan Corporation) and osmotic pumps (Searle’s Covera-HS tablets, Alza). Verelan contains a mixture of rapid and slow release beads [127] coated by a polymeric film consisting of a hydroxypropyl methylcellulose/ethylcellulose blend that is applied in standard coating pan by spraying the coating suspension onto the core beads. The final commercial capsules, containing 20% uncoated beads and 80% coated beads, show a totally pH-independent release kinetics [128].

Theophylline Diffusion Coefficient Calculated according to the Linear (Equation 15.80) ($D_{LIN}$) and Numerical ($D_{NUMERIC}$) Model Data Fitting

<table>
<thead>
<tr>
<th>$T$ (°C)</th>
<th>No.</th>
<th>%P</th>
<th>$D_{LIN} \times 10^6$ (cm$^2$/s)</th>
<th>$t_r$ (s)</th>
<th>$D_{NUMERIC} \times 10^6$ (cm$^2$/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>1</td>
<td>1</td>
<td>5.6 ± 0.34</td>
<td>90.6</td>
<td>5.6 ± 0.35</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td>66.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2</td>
<td>4.3 ± 0.43</td>
<td>141.7</td>
<td>4.2 ± 0.46</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td></td>
<td></td>
<td>165.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>4</td>
<td>5.0 ± 0.70</td>
<td>270.0</td>
<td>5.1 ± 0.64</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td></td>
<td></td>
<td>185.9</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>7</td>
<td>1</td>
<td>4.3 ± 0.59</td>
<td>38.2</td>
<td>4.3 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td></td>
<td></td>
<td>51.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>2</td>
<td>4.5 ± 0.21</td>
<td>154.1</td>
<td>4.4 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td></td>
<td></td>
<td>133.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>4</td>
<td>4.2 ± 0.11</td>
<td>167.1</td>
<td>4.2 ± 0.12</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
<td></td>
<td>194.6</td>
<td></td>
</tr>
</tbody>
</table>


$t_r$ is the empirical lag time calculated according to the linear model (Equation 15.80) data fitting; $T$ is the temperature; and %P is the polymer percentage in the membrane.
achieved by the presence of an interposed membrane (enteric coating material) between the drug active core and the semi-permeable membrane (cellulose acetate, hydroxypropylcellulose, polyethylene glycol). Indeed, the osmotic mechanism does not start until the GI tract water has completely dissolved the enteric coating material.

Nifedipine, another antihypertension drug belonging to the calcium channel blockers, is poorly soluble in water. Accordingly, an effective administration of this drug must be based on erosion or osmotic pressure mechanism. While the osmotic pump (Procardia XL tablets) device adopts the same membranes seen in verapamil release (Covera-HS), the erosion-driven delivery consists of a compress-coated system. The inner portion (core) contains micronized nifedipine plus various excipients (among which lactose, corn starch, microcrystalline cellulose), while the external membrane is made up of hydroxypropylcellulose, lactose, and nifedipine. As soon as this delivery system is put in contact with the release environment, the hydroxypropylcellulose hydrates and the soluble lactose erodes allowing nifedipine release at a constant rate. After, ~8 h, the external membrane is completely dissolved, and the immediate dissolution of the inner core takes place, this yielding to a very fast release of the remaining nifedipine dose.

Another interesting application of membranes is shown in the work of Järvinen and coworkers [13] who study drug release from pH and ionic strength responsive PAA grafted PVDF membrane bags in vitro. Square-shaped bags (2 cm × 2 cm) are formed by placing two PVDF membranes (Millipore; pore size 0.22 µm) on top of each other and hot-sealing three sides to get a membrane bag. The open side serves to insert the model drug inside the bag after grafting. Bags are irradiated with 25 kGy under nitrogen atmosphere, and the unsealed side is protected with a copper plate to avoid hot-sealing after grafting. Immediately after irradiation, bags are immersed at room temperature in a graft solution containing AA that is continuously purged with nitrogen in order to remove oxygen. Then bags are Soxhlet extracted with water to remove any remaining monomer and dried overnight. Finally, bags are filled manually with model drug (FITC-dextran), and the open side is seal. The USP 23 rotating basket method (100 rpm, 37°C, 900 cm³ of dissolution medium; 6 mM phosphate buffer at pH 2.0 or 7.0; the ionic strength is adjusted to 0.15 with NaCl) is used to study release kinetics from bags. Figure 15.8 shows that FITC-dextran release is considerably higher at pH 2.0 than at pH 7.0. Indeed, this is due to changes in the conformation of the grafted PAA chains as a function of pH. As PAA pKₐ is about 4 [129], at pH 2.0, polymer chains are undissociated, this resulting in a compact conformation. Accordingly, the pores of the PVDF-PAA membrane are open, and the drug can pass through. On the contrary, at pH 7.0, PAA molecules are dissociated, this yielding to a very fast release of the remaining nifedipine dose.

Release of FITC-dextran from membrane bags prepared from 50 wt% PAA grafted PVDF membranes into dissolution medium at pH 2.0 (filled circles) and pH 7.0 (open circles). (From Järvinen, K. et al., Pharm. Res., 15(5), 802, 1998. With permission.)

Another interesting application of membranes is shown in the work of Järvinen and coworkers [13] who study drug release from pH and ionic strength responsive PAA grafted PVDF membrane bags in vitro. Square-shaped bags (2 cm × 2 cm) are formed by placing two PVDF membranes (Millipore; pore size 0.22 µm) on top of each other and hot-sealing three sides to get a membrane bag. The open side serves to insert the model drug inside the bag after grafting. Bags are irradiated with 25 kGy under nitrogen atmosphere, and the unsealed side is protected with a copper plate to avoid hot-sealing after grafting. Immediately after irradiation, bags are immersed at room temperature in a graft solution containing AA that is continuously purged with nitrogen in order to remove oxygen. Then bags are Soxhlet extracted with water to remove any remaining monomer and dried overnight. Finally, bags are filled manually with model drug (FITC-dextran), and the open side is hot-sealed. The USP 23 rotating basket method (100 rpm, 37°C, 900 cm³ of dissolution medium; 6 mM phosphate buffer at pH 2.0 or 7.0; the ionic strength is adjusted to 0.15 with NaCl) is used to study release kinetics from bags. Figure 15.8 shows that FITC-dextran release is considerably higher at pH 2.0 than at pH 7.0. Indeed, this is due to changes in the conformation of the grafted PAA chains as a function of pH. As PAA pKₐ is about 4 [129], at pH 2.0, polymer chains are undissociated, this resulting in a compact conformation. Accordingly, the pores of the PVDF-PAA membrane are open, and the drug can pass through. On the contrary, at pH 7.0, PAA molecules are dissociated and swollen so that pores are partially blocked and drug passage is hindered. On the same principle, it is based on the application of Li and D’Emmanule [130] who synthesized cross-linked poly(NIPAAm) hydrogel (thermosensitive polymer) within the pores of sintered glass filter disks using an in situ free radical polymerization method. At 40°C, poly(NIPAAm) is in the shrunk state so that pores are open and model drug (salicylic acid) permeation is high. On the contrary, at 20°C, poly(NIPAAm) is in the swollen state, and pores are filled with the gel that hinders model drug (salicylic acid) permeation. In this manner, these authors can control drug release kinetics acting on temperature.

The aim of this section is to illustrate some coating techniques based on physical and physicochemical principles. In addition, for their potentiality, the attention will be then focused on asymmetric membranes and on membranes devoted to colon-specific delivery systems.

15.4.1 Membranes for Physically Coated Systems

Typically, aqueous and organic techniques can be used to coat solid dosage forms. In general, the choice of aqueous polymer dispersions implies various advantages, such as reduced toxicity and lower processing times, with respect to organic polymer solutions. In addition, aqueous approach, despite much higher polymer concentration, yields to coating formulation characterized by relatively low viscosities compared to those of the respective organic coating solutions. However, aqueous approach suffers for sensitivity to several factors such as temperature, pH, addition of electrolytes, and other polymers that, potentially, can lead to dispersion destabilization and coagulation. Obviously, coating properties coming from aqueous or organic techniques are neatly different, and this, in turn, is the result of different film formation mechanisms. In the organic solution, macromolecules, highly mobile and interpenetrated (spaghetti-like configuration), undergo sol–gel transition upon solvent evaporation to get film formation. Accordingly, homogeneous and compact films are produced. On the contrary, in the aqueous strategy, polymer particles are dispersed in the liquid, and upon water evaporation, they get together on the dosage form solid surface to form close-packed arrays. Capillary forces then drive the particles to coalesce together. Usually, the addition of a plasticizer is required to minimize film formation.
temperature, making particles softer and facilitating their coalescence. Consequently, film microstructure differs from that of organic-based film, and crack formation is, generally, more probable [131].

In both the organic and aqueous approach, release kinetics from coated systems is not an easy process as many variables, such as water diffusion, polymer swelling and dissolution, drug dissolution, diffusion, and crack formation through the coating, can play a key role [132]. In addition, the use of polymer blends in coating formation, although allowing a broad variety of drug release patterns, makes the release kinetics scenario much more complicated. Indeed, nowadays, limited knowledge is yet available on the importance of the coating technique strategy (aqueous or organic) in the case of polymeric blends. Nevertheless, it seems clear that, in blend coatings, the effect of film formation mechanism on film structure and thus on release kinetics is more important than in the case of one polymer coating [133].

For example, Lecomte and coworkers [131] study the characteristics of propanolol hydrochloride (Abbot, Ludwigshafen, Germany) loaded pellets (1.0%, w/w, loading) coated by a blend of water-insoluble (ethyl cellulose [EC]; Ethocel Standard 10 Premium, Dow Chemical Company, Midland, MI) and water-soluble (methacrylic acid–ethyl acrylate copolymer 1:1, Eudragit L100-55, Röhm, Darmstadt, Germany). Triethyl citrate (TEC, Morflex, Greensboro, NC) is used as plasticizer. Drug-loaded pellets are coated by EC and Eudragit L100-55 hydroscopic solutions and blends or by the respective aqueous polymer dispersions. EC/Eudragit L blend ratios investigated are 0:100, 25:75, 50:50, and 100:0 (w/w), while 0.1 M HCl and phosphate buffer pH 7.4 are the release environments considered in the USP XXV paddle apparatus (37°C). Spraying technique is used to coat the loaded pellets. In virtue of the higher degrees of entanglements, dry films coming from organic solutions show better mechanical properties (energy at break and elongation) for all the blend ratios considered. In addition, dry film mechanical properties do not sensibly depend on plasticizer content. For what concerns release properties, the authors find that release kinetics strictly depends on the coating technique considered (organic or aqueous) and a great variety of release patterns can be obtained by varying blend ratios. In particular, for organic coating, release kinetics increases with Eudragit L content, and it is improved by higher pH values. Conversely, in the case of aqueous coating, if pH increase still reflects in improved release kinetics, the effect of Eudragit L content on release kinetics is no longer (increasing) monotone. Finally, wherever at low pH release kinetics from aqueous coating is higher than the organic coating one, these differences practically vanish at high pH where the most important aspect is enteric polymer dissolution.

On the other hand, Stepmann and coworkers [132] focus the attention on release kinetics from aqueous coating technique. In particular, theophylline pellets (≤800 μm diameter; Boehringer Ingelheim, Ingelheim, Germany) coated by two different kinds of water-insoluble and enteric polymer ((1) EC [Aquacoat® ECD, FMC c/o Interorgana, Köln, Germany] and hydroxypropyl methylcellulose acetate succinate HPMCAS [ShinEtsu c/o Syntapharm, Mülheim and er Ruhr, Germany]; (2) EC and Eudragit L30D-55 [Röhm, Darmstadt, Germany]) are considered. TEC (Morflex, Greensboro, NC) is used as plasticizer. Blend ratios and release apparatus are similarly used by Lecomte et al. [131] and are mentioned previously. At low pH, the authors find that release kinetics from EC/Eudragit L- and EC/HPMCAS-coated pellets is similar and it increases with HPMCAS or Eudragit L content, respectively. At high pH, regardless coating type, release kinetics is improved due to the partial dissolution of the enteric polymer. Nevertheless, this is more evident in the EC/Eudragit L coating irrespective of blend ratio. The authors demonstrate that this is due to the higher presence of water-filled cracks in the EC/Eudragit L coating. This affirmation is also supported by mechanical tests on films exposed to high pH release environment (higher energy required to break EC/HPMCAS films).

It is now interesting to focus the attention on the different techniques used in the coating process. Typically, it involves deposition of uniform polymeric membrane onto the surface of the substrate such as tablets, pellets, or drug particles. Film coating, layering coating, and compressed coating represent the most used techniques [128]. Film coating process is performed in a coating pan, a fluidized bed, or a rotary granulator. Ethylcellulose, methacrylic ester copolymers, methacryl ester copolymers, cellulose acetate, and enteric polymers are widely used either alone or in combination with water-soluble polymers for the preparation of controlled release films. Since the integrity of the film and the absence of flaws or cracks are important factors in controlling the drug release kinetics from such preparation, it is very important that film formulation is optimized. In this light, plasticizers are often added to increase flexibility and to reduce the incidence of flaws. Obviously, coating properties strongly depend also on the presence of pigment and solvent and on process variables such as temperature and spray rate. Layering coating is often performed in a fluidized bed in a noncontinuous manner. In coating beads, for instance, the seeds may firstly be coated with one layer of active drug and then coated with one polymeric layer followed by another active drug layer to get a wafer structure. In some cases, the active drug may be dissolved or dispersed with the coating materials. Compression coating process is performed using a tablet press to make a compress coat surrounding a tablet core (tablet-in-tablet). The compress coat can act as a barrier to drug release or as a part of formulation to provide biphasic release. The process requires to initially compress the core formulation to get a relatively soft tablet that is then transferred in a larger die for final compression of the compress coat layer. This process can be used to develop a controlled release system with unique release profiles or to formulate two incompatible drugs by incorporating one in the core and the other in the compress coat layer.
granulation, drying, lubrication, and compression. In addition, it is less operator dependent, and it is continuous and is considerably fast. The principle of electrostatic deposition is based on the fact that opposite charges attract. Material deposition occurs when a pattern of charges is established on the substrate where the deposition is desired, and a supply of material to be deposited is delivered in the form of small, charged particles. The pattern of charges on the substrate will establish an electrical field, $E$, that interacts with charges on the material to be deposited according to Coulomb's law:

$$F = qE$$  \hspace{1cm} (15.82)

where

- $F$ is force
- $q$ is the charge

The charged particles will be moved by this force, transported to the substrate, and deposited in a pattern determined by the charge on the surface. The key components in the technology may be summarized as four main areas, namely, active pharmaceutical ingredients, substrate, electrostatic chuck, and the controlled field deposition process. For what concerns active ingredients, the technology allows the production of material with controlled size, morphology, uniform flow, and charging properties. Intrinsic surface properties of active ingredients can be modified to enhance charging and handling. The substrate, an insulating film, is defined as the base upon which the drug is deposited. The substrate mechanical properties, such as thickness, modulus, and strength, and the electrical property of bulk resistivity are critical [134]. A chuck is a clamp or a device that holds an object. The role of an electrostatic chuck is to hold the substrate and provide the charged pattern onto the substrate in this technology. The electrostatic chuck can be equipped with an electrode for sensing the number of particles attracted to the chuck, thereby ensuring an accurate amount of particles [135]. Finally, the charging is achieved by using a three-layer structure that has a conducting back-plane electrode, an insulating layer, and a patterned conducting top electrode. This controlled field deposition process enables the material to be directly deposited onto a single-layer substrate [136]. The electrostatic powder coating process implies electro-charged powder adhesion on a rotating charged cylinder. Then, the powder is put into close proximity to the tablets (to be coated) that are vacuum-held in depressions around another cylinder. An opposite charge is given to the powder by means of a high-tension electrode in order to transfer it to the exposed tablet surface. Powder fusion to form a film is achieved by brief exposure to a source of long-wave infrared radiation.

### 15.4.2 Membranes for Physicochemically Coated Systems

Differently to previous paragraph, in this case, coating process can also involve a chemical reaction, and this approach can be generally named as microencapsulation. Microencapsulated solid preparations are widely used in pharmaceutical, chemical, and other industries to protect various substances from environmental impact, as well as for extending their action [137]. In the pharmaceutical field, in particular, these preparations are mainly used to get controlled release drug kinetics, to minimize side effects, to reduce gastric irritations, and to mask the unpleasant taste of the contained drug [137–142]. Indeed, many different active components are microencapsulated: analgesics, antibiotics, antihistamine, cardiovascular agents, iron salts, antipsychotics [143], vitamins, peptides [144], proteins [145], antiasthma [140,146], bronchodilators, diuretics, anticancerogens, tranquilizers, and antihypertensives [137].

Basically, microencapsulation can be performed according to the interfacial polymerization technique and the coacervation/phase separation methods [137,147]. The first approach consists in the polymerization of a monomer at the interface between two immiscible phases yielding to the formation of a solid film surrounding the dispersed phase (termed microcapsule core or simply core). This technique applies in the case of water-immiscible liquid core and water-miscible liquid core and solid core. For instance, in the case of a water-miscible liquid core, a hydrophilic polymer aqueous solution is dispersed in an organic phase with the aid of an emulsifier to get a water-in-oil emulsion. The addition of a water-insoluble reactant in the organic phase promotes the polymerization and thus the formation of a solid film around the aqueous dispersed phase. As the penetration of reactants in the polymerization zone is easier in a liquid environment than in a solid one, interfacial polymerization is more suitable for liquid encapsulation. Typically, polyamide, polyester, and polyurethane films are realized by using various combinations of water- and oil-soluble monomers and solvents [147]. Microcapsule morphology is characterized by a continuous and smooth external film, whereas an inner irregular surface is general encountered. Microcapsules of 20–30 μm diameter (even if smaller 3–6 μm diameter capsules can be produced) characterized by a 20 nm film thickness can be obtained.

The coacervation/phase separation methods can be divided into aqueous and organic groups. In turn, aqueous group can be divided into complex and simple [137]. Simple coacervation, applying only for the microencapsulation of solid and liquid hydrophobic materials, implies the dissolution of a hydrophilic polymer in water where, subsequently, the hydrophobic core is dispersed. Encapsulation occurs due to the deposition of the coacervate (polymeric colloidal phase) on the hydrophobic core following a variation in temperature/pH or the addition of a precipitating agent. While complex coacervation differs from simple coacervation for the presence of more than one colloid, organic coacervation is the inverse of the aqueous one. Indeed, in this case, the core is constituted by a water-soluble material, while the film is a hydrophobic material. Among the many polymers that are used in the coacervation technique, agar, albumin, alginates, chitosan, collagen, pectin, and starch can be remembered for what concerns natural polymers, while acrylic
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acid, cellulose derivatives, polyurethanes, polyamides, and polyvinylpyrrolidone represent the synthetic part. Typically, microcapsules ranging from 5 up to 5000 μm can be produced, while elastic or rigid and fragile or tough films can be obtained.

To achieve maximum efficiency from using microencapsulated particles, it is necessary to know the time needed to extract the solid phase out of the polymeric capsule. The extraction rate of active components through a polymeric coating depends on many factors such as the nature of the polymeric film binder, the conditions under which the coating was applied, its structure, thickness, and porosity [148]. As a consequence, to properly design these particular delivery systems, a deep knowledge of the release mechanism and of the drug–film physical properties is required [149,150]. Indeed, drug release occurs from an ensemble of polydispersed spherical particles constituted by an external polymeric film that can undergo both erosion and swelling upon contact with the release environment. In addition, drug dissolution in the inner core (in the case of solid core) and drug diffusion in the film concur to determine the release kinetics. Indeed, as soon as microparticles are put in contact with the release environment, the external fluid crosses the polymeric coating, progressively dissolves the drug core, and fills the inner void space generated by core dissolution. Consequently, the drug present in the inner solution moves through the polymeric film determining the increase of its concentration in the release environment. Thus, the drug is distributed among outer solution (release environment), polymeric coating, inner solution, and solid core. Despite the industrial relevance of microencapsulated delivery systems, no many authors matched the mathematical modeling of these systems, probably due its complexity. Nevertheless, some interesting examples can be found in literature [141,148,151,152].

15.4.3 ASYMMETRIC MEMBRANES

Asymmetric membranes are made up by a thin, dense skin layer supported by a thicker, porous substructure layer (Figure 15.9). Accordingly, they combine the high selectivity of dense membranes with the good permeability of porous membranes and thin dense membranes [153]. The technique used to produce these particular membranes implies the dissolution of the desired polymer in a solvent mixture composed by at least two solvents. One will be a good solvent for the polymer (more volatile solvent), while the other (less volatile solvent) will be a poor solvent (or nonsolvent) for the polymer. Upon evaporation, due to different solvent boiling point, the solution enriches in the less volatile solvent (poor solvent), this causing an abrupt precipitation of the polymer [154]. This technique (phase inversion) implies the transformation from a solvent continuous phase to a polymer continuous phase. Indeed, as soon as the drying process develops, from the original solvent phase, two interdispersed liquid phases grow up. Then, further drying leads to a primary and secondary gel. The initial solvent solution contains also a third solvent (pore former) that has a nonsolvent character for the polymer and that is nearly less volatile than the other two solvents. An alternative process implies polymer dissolution in a solvent system, film casting, and subsequently immersion into a quench bath of nonsolvent for polymer. The solvent of the first step is extracted from the cast polymer solution into the quench bath, which leads to the precipitation of the polymer in structured form. In order to infer the desired elasticity and to reduce the brittleness to asymmetric membrane, hydrophobic/hydrophilic plasticizers (glycerol, diethyl phthalate) may be added to the coating formulation.

In the delivery field, asymmetric membranes are typically employed as semipermeable membranes in osmotic controlled delivery systems. Even if the drug release mechanism is mainly governed by the difference in osmotic pressure between the environmental fluid and drug-containing core of the delivery system, the diffusion contribute through the membrane cannot, in principle, be neglected. As soon as the delivery system is put in contact with the external delivery environment, water penetrates the asymmetric membrane, dissolves the inner core soluble compounds (among which the drug and the osmotic agent), and pumps out drug solution through membrane pores due to increased internal pressure. As asymmetric membrane is not perfectly semipermeable, part of the drug can be delivered also by diffusion. Accordingly, the drug release rate \( \frac{dM}{dt} \) is given by

\[
\frac{dM}{dt} = \frac{dM_o}{dt} + \frac{dM_d}{dt}
\]

(15.83)

where

- \( t \) is time
- \( M \) is the total drug amount released until \( t \)
- \( M_o \) and \( M_d \), are, respectively, the \( M \) contribute due to osmotic pressure difference and diffusion
According to Equations 15.35 and 15.3, Equation 15.83 becomes

\[
\frac{dM}{dt} = \frac{A}{h} k\Delta \pi c + AD \frac{c}{h}
\]  

(15.84)

where

- \( A \) and \( h \) are, respectively, device surface area and membrane thickness
- \( k \) is membrane permeability (with respect to water)
- \( \Delta \pi \) is osmotic pressure difference
- \( c \) is the dissolved drug concentration in the core fluid, while \( D \) is drug diffusion coefficient inside the asymmetric membrane

With respect to other osmotic technologies, asymmetric membranes ensure higher water permeability, this reflecting in the possibility of a greater designing flexibility. Indeed, faster release rate can be achieved and lower solubility drugs can be considered. Then, not only membrane porosity can be controlled by choosing the proper pore former, but also asymmetric membranes can be produced by means of conventional pharmaceutical equipment [153]. Typically, polymers such as cellulose derivatives, polysulfones, polyamides, polyurethanes, polypropylene, poly(vinyl chloride), polyvinyl alcohol, PVDF, ethylene vinyl acetate, ethylene vinyl alcohol, and poly(methyl methacrylate) are used to fabricate asymmetric membranes [155]. On the technological side, it has to be remembered that asymmetric membranes can be used to produce capsule shells and tablets by dip coating process followed by immersion into a quench bath or air drying process [155]. In addition, they can be used to coat beads (\( \approx 1 \) mm diameter) by means of the spray drying and conventional spray coating technique.

An interesting study about in vitro and in vivo performance of asymmetric membranes is given by Thombre and coworkers [156]. These authors, starting from a standard coating solution (cellulose acetate 15%, acetone 49%, ethyl alcohol 28%, and glycerin 8% [plasticizer, variable 0%–8%], TEC [variable 0%–8%]), manufacture capsules, filled by drug, according to a dip coating process [157]. The in vitro dissolution tests are performed using standard USP dissolution methodology (Apparatus 2, rotating paddles, 50 rpm, 37°C, and 900 or 1000 mL of medium). The pharmacokinetic studies are performed in four fasted and fed laboratory beagle dogs using an immediate release tablet as the control. In vitro results clearly evidence how the more soluble the drug the higher the release rate. In addition, the authors observe that membrane permeability decreases with increasing TEC concentration. Indeed, higher amount of TEC reflects in a thicker dense membrane layer. This aspect is well documented in Figure 15.10, showing the percentage of glipizide released from capsules characterized by an increasing TEC concentration. For the in vivo performance of asymmetric membranes (the same composition of in vitro test apart from the percentage of glycerin 3% and TEC 5%), doxazosin (1.5 mg dose) is used as a model drug. Figure 15.11 shows the comparison between mean plasma concentration due to standard immediate release tablets used as the control (std tablet) and asymmetric membrane capsules (AM capsules). Four laboratory beagle dogs in fed and fasted conditions are considered. It is clear that AM capsules alter doxazosin pharmacokinetics by reducing the concentration peak and prolonging absorption (\( T_{\text{max}} = 59.0 \) h fasted and 7.0 h fed).

15.4.4 Membranes for Colon Delivery

Membranes play a fundamental role also in the colon-specific drug delivery systems. This administration route, whose advantages have been well recognized and documented [158], provides more effective therapy of colon-related diseases such as irritable bowel syndrome and inflammatory bowel disease (IBD) including Crohn’s disease and ulcerative colitis.
Colon-specific delivery has the potential to address important unmet therapeutic needs including oral delivery of macromolecular drugs. The colon is also viewed as the preferred absorption site for oral administration of protein and peptide drugs because of the relatively low proteolytic enzyme activities in the colon. For example, insulin, calcitonin, and vasopressin can be absorbed in that region [159]. Because of the distal location of colon in the GI tract, a colon-specific drug delivery system should prevent drug release in the stomach and small intestine and effect an abrupt onset of drug release upon entry into the colon. This necessitates a triggering element in the system that can respond to physiological changes in the colon. Basically, the traditional four approaches to colon delivery are prodrugs, pH-dependent systems, time-dependent systems, and microflora-activated systems [158]. Membranes, typically, are involved in the last three situations. For example, Liu Xing and coworkers [160] studied the delivery of bee venom peptide loaded on liposomes contained in a Eudragit S100 coated calcium alginate beads. Drug release studies are carried out using a USP dissolution rate test apparatus (apparatus I, 100 rpm, 37°C). The coated calcium alginate gel beads are tested for drug release for 2 h in 0.1 M HCl (250 mL), as the average gastric emptying time is about 2 h. Then, the dissolution medium is replaced with pH 6.8 phosphate buffer (250 mL) and tested for drug release for 3 h, as the average small intestinal transit time is about 3 h. Next, pH 7.4 phosphate buffer (250 mL) is used to test for drug release for 3 h. As Eudragit S100 dissolves at pH ≥6.8, it is expected that peptide release takes place only after 2 h. Indeed, after coating dissolution, gel beads are exposed to the aqueous environment that promotes polymer matrix swelling and erosion, this leading to the liposome-loaded peptide release. Figure 15.12 shows that while the initial release of bee venom from the coated gel beads is very low, it considerable increases later on. Bee venom release in the first 2 h is negligible (pH 1.2), while the fractional drug amount released rises to 5.5% after 3 h and 16% after 4 h. After 8 h, about 90% is released. Siew and coworkers [161] study 5-aminosalicylic acid release from amylose–ethylcellulose coated pellets in batch culture fermentation systems containing amylase enzymes or fecal bacteria. The pellets (100 g batch size) are coated in a fluidized bed coater (GPCG-1 Uni Glatt, Glatt GmbH, Binzen, Germany) using an amylose–ethylcellulose mixture containing 50% amylose to a total weight gain of 15%. The mixture is sprayed at a rate of 0.3 g/min through a 1.1 mm nozzle under a pressure of 2 bar. The bed temperature is maintained at 40°C. These authors find that the rate of release of 5-aminosalicylic acid is slightly faster in the fecal fermentation system than in the enzyme system, although release in both systems is substantially faster than in the control. This proves that the amylose coating can be destroyed by the presence of proper enzymes that can be produced by fecal bacteria. These findings are substantially confirmed both in vitro and in vivo (four healthy volunteers) also by Macleod and coworkers [162] who work on pectin–chitosan–hydroxypropyl methylcellulose (3:1:1) film-coated radiolabeled (99mTc) tablets. For both in vitro and in vivo tests, tablets are provided by an outer enteric coating (hydroxypropyl methylcellulose phthalate). The GI transit of the tablets is assessed by gamma scintigraphy while a Calleva® dissolution apparatus is used for in vitro release (pectinolytic enzyme is added to Sorensen’s phosphate buffer to mimic colon environment). The experimental results show that tablet breakup starts once tablets are in the colon, due to degradation of the coating by colonic bacteria. Basically, this example falls in the so-called CODES™ approach [158] that couples the action of outer pH-sensitive coatings and an inner bacteria degradable coating as illustrated in Figure 15.13. Three polymeric layers surround the tablet core. The first coating (next to the core tablet) is an acid-soluble polymer (e.g., Eudragit® E),


![FIGURE 15.13] CODES approach mechanism of action. (From Yang, L. et al., Int. J. Pharm., 235, 1, 2002. With permission.)
and the outer coating is enteric with an HPMC barrier layer in between to prevent any possible interactions between the oppositely charged polymers. The core tablet is comprised of the active, one or more polysaccharides and other desirable excipients. The polysaccharides, degradable by enterobacteria to generate organic acid, include mannitol, maltose, stachyose, lactulose, and fructooligosaccharide. During its transit through the GI tract, CODES remains intact in the stomach due to the enteric protection, but the enteric and barrier coating will dissolve in the small intestine, where the pH is above 6. Because Eudragit E starts to dissolve at pH ≤5, the inner Eudragit E coating is only slightly permeable and swellable in small intestine. Upon entry into the colon, the polysaccharide inside the core tablet will dissolve and diffuse through the coating. The bacteria will enzymatically degrade the polysaccharide into organic acid. The consequent pH lowering is sufficient to affect the dissolution of the acid-soluble coating and the following drug release.

Among newly developed colon-specific drug delivery systems, pressure-controlled delivery capsules (PCDCs) [163] can be mentioned. Their mechanism of action is based on the relatively strong peristaltic waves taking place in the colon and leading to an increased luminal pressure. They consist of a capsular-shaped suppositories coated with a water-insoluble polymer (ethyl cellulose). Once taken orally, PCDCs behave like an ethyl cellulose balloon since the suppository base liquefies at body temperature. In the upper GI tract, PCDCs dissolve and leading to an increased luminal pressure. They consist of a capsular-shaped suppositories coated with a water-insoluble polymer (ethyl cellulose). Once taken orally, PCDCs behave like an ethyl cellulose balloon since the suppository base liquefies at body temperature. In the upper GI tract, PCDCs dissolve and diffuse through the coating. The bacteria will enzymatically degrade the polysaccharide into organic acid. The consequent pH lowering is sufficient to affect the dissolution of the acid-soluble coating and the following drug release.

The reabsorption of water in the colon provokes an increase of the luminal content viscosity. As a result, increased intestinal pressures directly affect the system via colonic peristalsis. Consequently, PCDC rupture and drug release in the colon take place.

### 15.5 TRANSDERMAL DELIVERY SYSTEMS

As the skin is one of the most readily accessible organs of the body, topical application of drugs for treatment of skin diseases or pathology has for a long time studied [164]. Indeed, the skin separates the vital organs from the outside environment and serves as a protective barrier against physical, chemical, and microbial attacks. Through these good protective properties, often topical applications represent a successful drug delivery strategy. Indeed, for many drugs, the transdermal route has the potential to be an extremely efficient delivery site [165]. Topical application avoids the effects of both gastric degradation and hepatic first-pass metabolism; it presents a large surface area for absorption (~2 m²) and has relatively low proteolytic activity [165]. Accordingly, today, there exist a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, estradiol, oxybutynin, scopolamine, and testosterone [166,167]. There are also combination patches for contraception as well as hormone replacement (see Table 15.3). In addition, transdermal administration can represent an opportunity to avoid side effects as it happens in the case of estradiol patches (used by more than a million patients annually) that, in contrast to oral formulations, do not cause liver damage [168]. Similarly, transdermal clonidine, nitroglycerin, and fentanyl patches exhibit fewer adverse effects than conventional oral dosage forms. Despite this encouraging frame, however, some

<table>
<thead>
<tr>
<th>Drug</th>
<th>Product Name</th>
<th>Dose and Patch Size</th>
<th>Dose Delivered</th>
<th>Clinical Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>Catapres-TTS</td>
<td>2.5–7.5 mg in 3.5–10.5 cm²</td>
<td>0.7–2.1 mg in 7 days</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Ethinyl estradiol (EO)</td>
<td>Ortho-Evra</td>
<td>0.75 mg EO and 6 mg N in 20 cm²</td>
<td>0.14 mg EO and 1.05 mg N in 7 days</td>
<td>Birth control</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Scopolamine</td>
<td>0.14 mg EO and 1.05 mg N in 7 days</td>
<td>1.8–7.2 mg in 3 days</td>
<td>Analgesia</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Oxytrol</td>
<td>10–32 mg in 12 h</td>
<td>10–32 mg in 12 h</td>
<td>Postherpetic neuralgia</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Nitroglycerin</td>
<td>0.14–0.20 mg O and 1.05 mg N in 7 days</td>
<td>0.14–0.20 mg O and 1.05 mg N in 7 days</td>
<td>Dermal anesthesia</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Fentanyl</td>
<td>0.7–2.1 mg in 7 days</td>
<td>0.7–2.1 mg in 7 days</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Lidocaine</td>
<td>0.39–0.7 mg EO and 1.05 mg N in 7 days</td>
<td>0.39–2.1 mg in 7 days</td>
<td>Angina</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Scopolamine</td>
<td>0.42–1.0 mg N in 3–4 days</td>
<td>0.42–1.0 mg N in 3–4 days</td>
<td>Hormone replacement</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Testosterone</td>
<td>1.0 mg in 1 day</td>
<td>1.0 mg in 1 day</td>
<td>Overactive bladder</td>
</tr>
<tr>
<td>Testosterone</td>
<td>FemPatch</td>
<td>2.5 mg in 1 day</td>
<td>2.5 mg in 1 day</td>
<td>Motion sickness</td>
</tr>
</tbody>
</table>

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problems connected with the transdermal route still remain. Indeed, only low-molecular-weight (MW <500), high lipophilicity (oil soluble), and small required dose (up to milligrams) drugs can be successfully administered. The smallest drug presently formulated in a patch is nicotine (MW = 162), and the largest is oxybutinin (MW = 359). Opening the transdermal route to large hydrophilic drugs is one of the major challenges in the field of transdermal drug delivery. Indeed, the possibility of releasing drugs such as proteins and peptides would lead to considerable advantages in terms, for example, of patient’s health and compliance. In this light, the most clinically significant protein is, of course, insulin. Due to the chronic nature and multiple-daily dosing requirement of its administration schedule and the population of diabetics in the world, providing a noninvasive delivery mechanism for this compound would represent a considerable improvement from both the patient and the manufacturer viewpoint. However, other macromolecules such as cyclosporin, luteinizing hormone-releasing hormone (gonadotropin-releasing hormone), and thyrotropin-releasing hormone could take advantage from a transdermal administration. Finally, also vaccines could be administered by means of the transdermal route, and this assumes a very important aspect if we remember that the World Health Organization currently recommends that children be immunized with around 12–13 different vaccines before 1 year of age, which, in addition to the discomfort associated with needle injections, also raises issues about the potential risk of transfer of blood-borne pathogens [165]. Accordingly, the possibility of delivering such large molecules through the skin in a painless way, and yet still achieve sufficient cellular response to elicit immune protection, would be very important. Fortunately, large molecules released through the skin may now be possible with some of the physical enhancement technologies. Consequently, the target of this section is to illustrate some examples of transdermal drug delivery focusing on passive diffusion-regulated delivery systems and systems aided by physical enhancing methods.

15.5.1 Membranes for Passive Delivery Systems

As the skin has evolved to impede the flux of toxins into the body and minimize water loss, it shows a very low permeability to the penetration of foreign molecules [169]. A unique hierarchical structure of lipid-rich matrix with embedded corneocyte in the upper strata (15 μm) of the skin—the stratum corneum (SC)—is essentially responsible for this barrier. The corneocytes, comprising cross-linked keratin fibers, are about 0.2–0.4 μm thick and about 40 μm wide [170]. They are held together by corneodesmosomes, which confer structural stability to the SC. The SC lipids are composed primarily of ceramides, cholesterol, and fatty acids that are assembled into multilamellar bilayers. This unusual extracellular matrix of lipid bilayers serves the primary barrier function of the SC. The layer of lipids immediately adjacent to each corneocyte is covalently bound to the corneocyte and is important in maintaining barrier function. The SC is continuously desquamated, with a renewal period of 2–4 weeks. It is actively repaired by cellular secretion of lamellar bodies following the disruption of its barrier properties or other environmental insults [171]. Due to its structural heterogeneity, solute transport in SC lipid bilayers is highly anisotropic and size dependent, and that is why spatial variations in solute partition and diffusion coefficients are often observed [172].

Just below SC, we can find the epidermis, a viable tissue devoid of blood vessels 50–100 μm thick. The inner skin layer is represented by the dermis (1–2 mm thick) containing capillary loops able to take up transdermally administered drugs for systemic distribution [166]. On the basis of its morphology, in principle, drug penetration through the skin can take place through sweat glands, hair follicles, and transdermally [173,174]. However, the contribution of follicles is hard to be quantified (in human skin, their contribution is negligible [174]) as their number per unit area is not equal for the different body parts both in humans and animals. Undoubtedly, based on surface area available to permeation, the diffusion mechanism through SC is the most relevant one, and that is why SC characteristics, often, discriminate between drugs that can take or cannot advantage from a purely diffusive transdermal strategy.

The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process involving (1) dissolution within and release from the formulation, (2) partitioning into the SC, (3) diffusion through the SC, principally via a lipidic intercellular pathway (i.e., the rate-limiting step for most compounds), (4) partitioning from the SC into the aqueous viable epidermis, (5) diffusion through the viable epidermis and into the upper dermis, and (6) uptake into the local capillary network and eventually the systemic circulation [175]. Therefore, an ideal drug candidate would have sufficient lipophilicity to partition into the SC but also sufficient hydrophilicity to enable the second partitioning step into the viable epidermis and eventually the systemic circulation.

Transdermal patches can be classified into two categories on the basis of their design: reservoir-type and matrix-type patches [166]. A reservoir-type patch consists of four major components: the reservoir, where drug is hosted in a solution or in a gel, the rate-controlling membrane, the adhesive layer and the backing. Drug release occurs due to drug permeation through the membrane and the adhesive layer to get skin surface. Typically, the reservoir contains also an enhancer, a chemical compound that is diffusing through the membrane and the adhesive layer and penetrates into the skin improving skin permeability to drug. A little variation of the reservoir-type patch is represented by the multilaminate design, where the drug is dispersed/dissolved in a solid polymer matrix [176]. By contrast, matrix-type patches, which were introduced after reservoir-type patches, combine drug, adhesive, and patch backing into a simpler design that does not involve a rate-controlling membrane. Accordingly, the skin permeability usually governs the rate of drug delivery. Although these patches are easier to fabricate, they have limited flexibility.
in their design compared with reservoir-type patches that also offer the advantage of higher formulation flexibility and tighter control over delivery rates. Obviously, reservoir-type patches usually involve greater design complexity. While reservoir-type patches can provide a constancy of drug release rate, meaning that the device can supply a constant amount of drug per unit time, this is not achievable in matrix-type patches. On the contrary, however, reservoir-type patches can have an initial burst of drug release. As membrane plays a fundamental role in reservoir-type patches, it must satisfy some requirements. In particular, a drug diffusion coefficient ranging from about $10^{-3}$ to $10^{-8}$ cm$^2$/s, the possibility of being fabricated in form of thin film, a low solubility for the drug, the property of being soft and well above shipping temperatures, and an elastic modulus of about 1000 Pa to 1 MPa constitute fundamental prerequisites. For example, polyethylene, ethylene vinyl acetate, and polyporplene films match the aforementioned requirements [176]. In general, however, ethylene vinyl acetate films represent the best candidates for these applications as vinyl acetate content can be modified to tune membrane permeability in relation to drug. In addition, membrane thickness, ethylene component crystallinity, and domain structure are other important variables to properly design release rate characteristics. For what concerns adhesives, they must be very permeable to both drug and enhancers as drug release rate is demanded only to membrane.

It is worth noticing that the principles ruling transdermal drug delivery are analogous to those occurring in ophthalmic lenses. Indeed, reservoir patches correspond to sandwich-type lenses [177], while matrix patches correspond to therapeutic lenses where the drug is combined with polymer [178].

### 15.5.2 Membranes for Physically Enhanced Delivery Systems

While chemical enhancers can be a successful tool for the improvement of small drug permeability through the skin, for big molecules, other strategies have to be undertaken. Indeed, protein and peptide transdermal administration requires the use of physical methods to enhance permeability. Basically, these methods comprehend electrically based techniques (iontophoresis, electroporation, ultrasound, photomechanical wave [PW]), structure-based techniques (microneedles), and velocity-based techniques (jet propulsion) [165]. Although a detailed description of all these techniques is out of the scope of this section, some details on electrically based systems can be useful in the light of membrane applications in the delivery field.

Iontophoresis was initially developed to facilitate the delivery of ionized solutes, with inherently low partition coefficients due to their charged state, across tissue membranes. The technique involves the application of a small electric current (usually 0.5 mA/cm$^2$) to a drug reservoir on the surface of the skin, with the same charged electrode as the solute of interest placed together to produce a repulsion effect that effectively drives solute molecules away from the electrode and into the skin [179] (Figure 15.14). The effect of simple electrorepulsion is known to be one of the main mechanisms by which iontophoresis produces its enhancement effects, although other factors such as a permeability increase of the SC due to an electric current flow and electroosmosis of uncharged and larger water-soluble molecules can play an important role [180]. If iontophoresis proved to be successful for low-molecular-weight drugs (MW <500) [165,179], also for macromolecules and proteins, encouraging results have been achieved. For this purpose, we can mention calcitonin (salmon) [181], corticotropin-releasing hormone [182], delta sleep-inducing peptide [183], dextran sulfate [184], insulin [185], growth hormone-releasing factor [186], leuprolide acetate [187], luteinizing hormone-releasing hormone [188], neutral thyrotropin-releasing hormone [189], oligonucleotides [190], parathyroid hormone [191], and vasoressin [192].

Electroporation is a technique that was initially developed for transmembrane delivery of macromolecules in isolated cells in culture systems and then expanded to intracellular...
delivery in vivo [193]. The process involves the application of large transmembrane voltages caused by electrical pulses (10 µs to 100 ms), which probably cause the formation of transient pores (Figure 15.15) in the membrane that subsequently allow the passage of macromolecules from the outside of the cell to the intracellular space via a combination of possible processes including diffusion, local electrophoresis, and/or electroosmosis [194]. The application of electroporation to the skin descends from the theory that the intercellular lipid bilayers of the skin behave like those of cell membranes and be susceptible to pore formation following high-voltage electrical pulsing [195] (Figure 15.15). The work of Prausnitz and coworkers demonstrates the effectiveness of electroporation in transdermal drug delivery [166]. While the electrical resistance of the skin is reported to decrease as much as three orders of magnitude within microseconds of administration of an electrical pulse [196], skin permeability to drugs is also reported to increase by several orders of magnitude. This is mainly attributed to electrophoretic movement and diffusion through the newly created aqueous pathways [197] (Figure 15.15). In vitro experiments proved the increase in transdermal penetration of up to 10⁴-fold not only for low-molecular-weight drugs but also for bigger drugs such as luteinizing hormone-releasing hormone [198], insulin [199], and oligonucleotides [200].

Ultrasound (or sonophoresis) is a technology more traditionally associated with the fields of physiotherapy, sports medicine, and medical imaging rather than transdermal drug delivery. Compared to physiotherapy, where high-frequency energy (1 MHz) is used, in transdermal drug delivery, low-frequency energy (20 kHz region) is applied across the skin.

FIGURE 15.15 Hypothetical bilayer poration model. Pores are hypothesized to form in the intercellular bilayers via momentary realignment of lipids that recover their original position at various times after the electrical pulse. (From Cross, S.E. et al., Curr. Drug Deliv., 1, 81, 2004. With permission.)

Cavitation, the acoustically induced formation and oscillation of gas bubbles formed because of the mechanical energy supplied, is the most probably explanation for skin permeability increase [201]. Indeed, bubble presence and movement produce defects large enough to facilitate the passage of macromolecules through the SC bilayers. Recent studies demonstrate an increase in 2.6–15-fold of estradiol, naphthol, aldosterone, lidocaine, and testosterone diffusion coefficient due to ultrasound.

PWs (also known as laser-generated stress waves) are the pressure pulses produced by ablation of a material target (polystyrene) by Q-switched or mode-locked lasers (Figure 15.16). Although the mechanism by which PWs increase the permeability of the SC is not entirely clear, microscopic studies have indicated that the energy supplied promotes the formation of transient channels through the SC. The PW delivery of insulin through the skin of diabetic rats was shown to cause reductions in blood glucose of around 80% ± 3% and was maintained below 200 mg/dL for more than 3 h. The largest molecule that has been reported to be delivered through rat skin to date has been 40 kDa [165].

15.6 NANOMEDICINE

Nanomedicine can be defined as the branch of medicine that takes advantage from nanotechnology. This means that nanomedicine implies the use of materials whose components exhibit significantly changed properties by gaining control of structures at the atomic, molecular, and supramolecular levels [202]. Accordingly, nanomedicine is related to the peculiar properties of nanosystems such as increased permeability through cellular membranes, facilitated spreading in the body, increased dissolution rate, and solubility in the liquid physiological environments. These two last properties are strictly
connected to the most intriguing aspect of nanosystems, that is, the effect of surface atoms/molecules on nanosystem’s behavior. Indeed, as nanosystems are characterized by a huge surface area, the ratio between surface and bulk atoms/molecules is no longer negligible as it happens in conventional systems. Thus, surface properties play an important role as discussed in the following paragraphs where the attention will be focused on two different applications of nanosystems: restenosis prevention and drug bioavailability enhancement.

15.6.1 Membranes and Restenosis

15.6.1.1 Clinical Problem: Artery Restenosis

The most common cause of artery occlusions (stenosis) is represented by the progressive development of atherosclerosis. When this occurs in coronary artery, serious health problems, which each year lead to a significant mortality worldwide [203], can take place. Since 1979, the revascularization of stenotic coronary arteries [204] has been obtained by a technique named percutaneous transluminal coronary angioplasty (PTCA). This is a nonsurgical method (Figure 15.17) that involves (1) advancing a balloon catheter to an area of coronary narrowing, (2) inflating the balloon, and (3) retrieving the catheter following balloon deflation.

Despite the efficacy of PTCA, this technique can induce the development of symptomatic re-occlusion (restenosis) caused by early elastic recoil, intimal hyperplasia, late constricting remodeling of the vessel [205], and formation of mural thrombus, in about 30%–50% of treated patients (Figure 15.18) [206]. To overcome these problems, PTCA has been associated with the deployment of a stent, an expandable metal tubular mesh (bare metal stents [BMS]) (Figure 15.19). BMS can reduce restenosis rate down to 20%–30% [207–209].

The partial success of BMS depends on the induction of the intimal hyperplasia; this is a phenomenon [205,210] mainly characterized by an excessive proliferation of vascular smooth muscle cells (VSMCs), which reside in the so-called media layer of the artery wall (Figure 15.20). VSMC proliferation, although reduced in extent, persists months after stent implantation and is paralleled by an increased production of extracellular matrix.

With the aim to overcome the excessive VSMC proliferation observed after BMS implantation, devices able to locally deliver antiproliferative drugs (drug-eluting stents [DESs]) have been developed (Figure 15.21). The most used antiproliferative drugs are sirolimus (Rapamycin®) and paclitaxel (Taxol®). The delivery of these antiproliferative drugs from DES reduces artery restenosis (down to 5%–10% of treated patients [211,212]) more efficiently than BMS. However, DESs did not completely solve the problem [213] as they can trigger unwanted side effects such as stent thrombosis (ST) and delayed restenosis compared to BMS [214,215].

15.6.1.2 Restenosis Prevention by NABD

The use of coronary stents following PTCA led to significant reductions in restenosis; despite this, some problems related to the increased risk of late ST have still to be solved [216,217]. In this regard, the design of novel stent is under active investigation [216,218,219]. In parallel, the identification of novel antiproliferative drug is being investigated.

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**FIGURE 15.18** Possible complications of PTCA. (From Califf, R.M., *Am. Heart J.*, 130, 680, 1995.)

**FIGURE 15.19** Endoarterial implantation of a BMS. (a) stent + balloon insertion, (b) balloon inflation and stent deposition, and (c) stent position in the coronary wall. (From http://www.medicinenet.com/images. Accessed April, 2012.)
With regard to the development of novel antiproliferative drug, an emerging class of molecules with potential therapeutic value is represented by the so-called nucleic acid–based drugs (NABD) [220]. These molecules include, among others, small interfering RNAs (siRNAs) and aptamers. They base their action mechanism on the ability to recognize, in a sequence-specific fashion, a target represented by an mRNA or a protein by siRNA and aptamers, respectively [221,222]. After establishing the link, these NABDs are able to induce either the destruction (siRNA) or the block of the biological functions (aptamers) of the target. Since the NABDs can be engineered to hit virtually any target, these molecules have a very wide applicability [220,221,223], including ISR [224].

siRNAs are short double-stranded RNA molecules (sense and antisense strands) 22 nucleotides long, capable of inducing the degradation of a specific homologue mRNA (Figure 15.22a); they can be of endogenous or exogenous origin [225,226]. To exert the biological role, the antisense strand of the siRNA needs to be embedded into a protein complex called RNA induced silencing complex (RISC) [227]. The RISC, guided by the short single-stranded RNA, can recognize a homologous region on the target RNA, thus triggering the catalytic cleavage of the target. This process has become more attractive for therapeutic applications after the demonstration that [228] siRNAs can specifically destroy a homologous mRNA in human cells. In the field of coronary restenosis prevention, we have evidence that siRNAs directed against the mRNA of the E2F1 and cyclin E genes, pivotal regulators of cell proliferation, resulted in a remarkable downregulation of human coronary smooth muscle cell proliferation in vitro. This effect is patient and transfectant independent, reversible, and effective in asynchronous and synchronous CSMCs and in normo- to hyperglycemia and does not induce cell death. Thus, our results provide the rationale for future experimentation in animal models aimed at the development of novel therapeutic approaches for hyperproliferative vascular diseases.

Aptamers [222] are short stretches of single-stranded DNA or RNA potentially able to recognize with high affinity any given molecular targets (Figure 15.22b), such as proteins and carbohydrates modulating their biological functions in an antagonistic or agonistic manner [229]. We tested the antiproliferative effects of a single-stranded DNA aptamer directed against the eukaryotic elongation factor 1A (eEF1A), a family of proteins firstly recognized as being involved in the correct positioning of the aa-tRNA in the A site of the ribosome; more recently, a direct role in the regulation of other biological processes including the control of cell cycle, growth, and death has been established. We have evidence that this aptamer can significantly reduce the expansion of prostate cancer cells [230]; studies are ongoing to test its ability to reduce the proliferation of VSMCs.

In spite of the high therapeutic potential of NABD, their clinical use is limited due to the lack of optimal delivery systems. Whereas in vitro NABDs show high biological effectiveness, in vivo they tend to have much lower effectiveness for several reasons such as (1) the degradation induced by nucleases present in the bloodstream, in the extracellular matrix, and in the intracellular environment [231]; (2) the difficulty in crossing cell membranes (due to the electrostatic repulsion between the negatively charged phosphate groups present on NABDs and the negatively charged cell membrane; additionally, the hydrophilic nature of the NABDs does not allow their passage through the hydrophobic core of the cell membrane);
Membranes in Drug Delivery and (3) the problems related to the cellular trafficking such as the release from endosomes and the cytoplasmic transport [232,233]. In addition to the aforementioned points, the local application of NABDs in artery vessels poses other problems, that is, the in situ positioning and the shear stress conditions determined by blood flow. It is therefore clear that if administered as naked molecules, only a minor fraction of NABD would reach the target resulting in negligible biological effects.

To try to overcome the limitation in NABD delivery to artery vessels, we and others are developing polymeric-based delivery approaches. Our strategy is based on the use of a matrix made up by Pluronic F127 (PF 127) mixed with alginate (Protanal 10/60) [234,235]. PF 127 is a synthetic poly(oxyethylene–oxypropylene) block copolymer that shows reverse thermoresponsive properties in aqueous solutions. In particular, it behaves as a low viscosity solution at room temperature, while, at higher temperature, it organizes into cubic liquid crystalline structures showing a gel-like mechanical behavior. This property makes PF 127 very attractive as, in principle, it can be combined with the NABD complexes by simple mixing at temperature around 4°C–8°C. Alginites, the second component of our mixture, are linear polymers whose respective units are represented by D-mannuronic (M) and L-guluronic (G) acid linked 1 → 4. In the presence of an aqueous solution containing bivalent cations, they form temperature-insensitive strong physical gels. Indeed, bivalent cations, interacting with oxygen of COO⁻ groups and some OH groups of guluronic residues belonging to different chains, take part to an interchain bond responsible for the formation of bond cavities. Sequences of these cavities form the so-called egg-box junction zones.

Just after stent positioning, we plan to apply the aqueous mixture PF 127/alginate/NABD to the endoluminal surface of the artery vessel; due to the body temperature (37°C), the PF127 undergoes gelation soon after in situ release. The inner surface of the gel-like matrix is then quickly exposed to a solution rich in bivalent cations, thus inducing the gelation of the alginate component (alginate/pluronic layer) (Figure 15.23). While the strong alginate part, facing blood flow, prevents from premature gel erosion and NABD migration toward the blood flow, the soft PF 127 portion, sandwiched between coronary wall and the strong part, allows NABD delivery to the coronary wall where VSMCs, the target cells, reside. The potential advantages of this gel paving stent technique over other approaches are (1) an easy and safe NABD loading within the gel matrix and (2) the opportunity of creating a physical barrier between the damaged coronary wall and the overflowing thrombogenic and inflammatory elements present in the blood stream. Additionally, by considering proper polymeric blends [234,235], it is possible to limit NABD release to the systemic circulation favoring NABD delivery to the target cells.

![FIGURE 15.22](image_url) siRNA and aptamer mechanisms of action: (a) siRNA induces target mRNA degradation guiding the catalytic protein complex RISC to an mRNA region complementary to the siRNA antisense strand; (b) aptamers alter protein activity by binding to the protein itself.

![FIGURE 15.23](image_url) Structure of the double-layered intravascular gel.
An additional level of complexity of our approach includes the possibility to embed NABDs into the polymer mixture not as naked molecules but instead as complexes with different carrier molecules. The complexation with carrier molecules can indeed improve the amount of molecules delivered, the stability, and permanence of the molecules in the diseased tissue and can allow a targeted delivery. In this last regard, an interesting strategy for minimizing NABD delivery to bystander tissues, which may be negatively affected by the NABD, is based on the use of agents that recognize specific molecules on the surface of distinct cell populations [236,237]. It is in principle possible to link to the NABD cell-specific ligands [237–242] to confer cell specificity to NABD delivery system. Specific interaction between a ligand and its cellular membrane receptor can enhance NABD cellular uptake by means of receptor-mediated endocytosis. In addition to conjugate the targeting molecule to the NABD, which in some case may be problematic due to interferences with the NABD biological activity, it is also possible to link the targeting molecule to the NABD delivery system, typically a nano-/microcarrier as detailed in the following.

Regardless of the type of targeting agent, carrier molecules can be subdivided into three classes on the basis of their characteristic length [243]: nano-, micro-, and macroscale vectors. In general, nanoscale vectors are represented by polycationic polymers or lipids that self-assemble with NABD to form polyelectrolyte complexes. Microscale vectors usually consist of NABD entrapped within a polymeric matrix, and macroscale vectors are 2D/3D scaffolds or matrices (mainly polymeric but not only) hosting the desired NABD. Of course, it is possible to embed nano-/microscale vectors inside macroscale vectors. Nano-/microscale vectors protect NABD and favor the cellular internalization, while macroscale vectors can modulate nano-/microscale vector release kinetics at the site of action (Figure 15.24).

The advantages of using combined delivery vectors include, among others, the possibility to improve localized NABD delivery. Indeed, if the macroscale vectors (typically matrices) are per se very useful and important in the NABD delivery field [244], their combination with nano-/microscale delivery systems can allow a precise designing of NABD release kinetics. Basically, controlled release of a solute from a matrix is due to matrix erosion or to matrix topology or to both of them [245]. In the first case (matrix erosion), the destruction of the matrix network is the leading cause of the drug release, while drug release due to migration through the matrix is negligible. In the second case (matrix topology), the driving force for drug release is based on the different concentration of the drug in the matrix and in the outside environment. Of course, delivery kinetics is highly affected by drug–network steric and physicochemical interactions, and, in this respect, the mean dimension of network meshes plays a predominant role. Finally, in the third case (matrix erosion and matrix topology), both aspects play an important role. Accordingly, a high level of release kinetics and pharmacological designing can be achieved by embedding different NABD-synthetic vector complexes inside the matrix. In the case of surface erosion–controlled matrices, it would be possible to get the simultaneous release of different complex types, each one optimized for the transfection of a particular cell type. Additionally, by a proper spatial loading (e.g., high complex concentration in the external matrix portion and a low concentration in the inner part), it would be possible releasing the attack dose followed by the maintenance one. In case of topology-controlled matrices, instead, release kinetics can be controlled by complex mobility inside the matrix.

In the system we propose for coronary vessel delivery, the macroscale vector is represented by the PF 127/alginate gel, while the nano-/microscale vector is composed by NABD complexed with different molecules including cationic liposomes. In our case, the idea is to have a matrix where diffusion of nano-/microscale vectors toward the diseased tissue (inner artery wall) is driven mainly by the different concentration of the drug in the matrix and in the outside environment (matrix topology).

The choice of the proper nano-/microscale carrier is crucial as the net superficial charge of the carrier/NABD complex plays a key role for what concerns extracellular barrier crossing. Indeed, if anionic and cationic complexes usually show good solubility and, thus, stability in the physiological environment, they present other drawbacks. Anionic complexes, in principle, cannot transflect cells in virtue of the electrostatic repulsion with the negatively charged cell membrane. Conversely, cationic complexes bind to cell membrane due to strong electrostatic interactions leading to nonspecific cellular uptake through adsorptive endocytosis [246]. Unfortunately, however, this strong interaction can cause membrane disruption and consequent cell death. In addition, the presence of negatively charged blood proteins can induce the formation of complex-protein aggregates that are no longer soluble and precipitate. These precipitates are then cleared by phagocytic cells [247]. Whereas neutral complexes are not affected by the aforementioned problems, in the physiological environment, they tend to associate each other resulting in a limited solubility. Currently, we are exploring the use of cationic lipids as micro-vectors for NABD, and as an alternative, NABD directly linked to lipid molecules will be also tested.

![FIGURE 15.24 Combination of macro- and nano-/microscale delivery carriers for NABD delivery.](image-url)
In conclusion, our and other approaches are expected to further improve the efficacy and specificity of action of current available strategies to ISR. Given the complexity of the problem, it is clear that only multidisciplinary approaches with the contribution of engineers/biologists/medical doctors can have the possibility to successfully solve this relevant health problem.

15.6.1.3 Mathematical Modeling
As one of the key points guaranteeing the reliability and the effectiveness of the gel paving approach consists in ensuring a drug release kinetics able to account for the pathobiological events characterizing restenosis (see Section 15.6.1.1), a detailed theoretical designing is required. Among the many works devoted to this topic [248], we would like to remember that of Davia and coworkers [218] as it accounts for the simultaneous presence of the gel layer and the stent. In this work, it is assumed that the fate of a drug molecule diffusing from the gel layer toward the coronary wall depends on many factors. The first one is drug mobility (diffusion coefficient) in the gel layer. Then, inside the intima, drug movement is essentially due to diffusion, induced by the concentration gradient, and convection, generated by the a radial hydrostatic pressure gradient between lumen and coronary wall [249]. In order to reach the media (the middle arterial wall layer), the drug molecule must partition from the intima to the internal elastic lamina and then to the media. Again, diffusion and convection govern drug motion even though drug binding to proteins and metabolism can be important. While drug binding to proteins is reversible, metabolism (here meant as cellular internalization) is irreversible and leads to drug disappearance. In this context, arterial wall can be schematized as an inter-channeled structure (porous medium) where free drug molecules, moving in the fluid filling the channels, progressively bind to proteins and are metabolized [250]. Again, drug molecule transport to adventitia (the outermost arterial wall layer) requires two further steps: media—external elastic lamina—adventitia. Once in the adventitia, the molecule is swept out by vasa vasorum, lymphatic drainage, and lost into connective tissues. In the light of this physiological frame and the symmetry of the problem (drug movement can occur only the axial, , and radial, , directions), the governing equation ruling drug transport accounts for diffusion in the axial and radial directions, convection in the radial direction, and internalization in the coronary wall:

\[
\frac{\partial C_i}{\partial t} = D_i \frac{\partial}{\partial z} \left( \frac{\partial C_i}{\partial z} \right) + D_i \frac{\partial}{\partial r} \left( r \frac{\partial C_i}{\partial r} \right) - v_r \frac{\partial C_i}{\partial r} - kC_i \quad (15.85)
\]

where

- \( t \) indicates time
- \( C_i \) and \( D_i \) are, respectively, the drug concentration and diffusion coefficient in the layer \( i \) (gel layer or coronary wall)
- \( v_r \) is the constant radial convection velocity (it is assumed zero in the gel layer and in all the coronary wall portions shielded by gel; see Figure 15.23), while \( k \) is the internalization constant

Once the proper initial conditions (drug concentration is zero in the artery wall and uniform in the gel layer) and boundary conditions (drug concentration is zero in the blood, and in the adventitia external surface, drug flux is zero on the stent strut surface) are set, Equation 15.85 numerical solution provides the progressive drug spreading in the coronary wall. One of the most important conclusions of Davia’s work [218] consists in the necessity of disposing of drug molecules of different mobility to hinder both the fast and slow events characterizing the restenosis cascade events (see Section 15.6.1.1). In the case of NABD (see Section 15.6.1.2), this means that part of the NABD dose has to be complexed by a big complex (e.g., liposomes) and the remaining part by a small complexing agent (e.g., cholesterol). In this manner, the NABD fraction complexed by the small carrier, being much more mobile, is firstly released and hinders the fast pathobiological events. On the contrary, the fraction complexed by the big carrier, being much less mobile, is subsequently released and acts against the slow pathobiological events.

15.6.2 Polymeric Membranes and Drug Nanocrystals

15.6.2.1 Physical Background
It is well known that the solubility, melting temperature, and enthalpy depend on crystal radius (assumed, for the sake of simplicity, of spherical shape) [252,253]. In particular, crystal radius decrease reflects in melting temperature/enthalpy decrease and in solubility increase. The physical explanation of these phenomena relies on the different properties of surface and bulk atoms/molecules. Indeed, as surface atoms/molecules are in a less confined arrangement (fewer inter-atomic bonds) with respect to bulk atoms/molecules, they are characterized by a higher energetic state than bulk atoms/molecules. Accordingly, lattice breakdown on crystal surface requires less energy, and it is favored with respect to bulk lattice breakdown. This theoretical interpretation is supported by the work of Huang and coworkers [253] who, on the basis of experimental data and molecular dynamics simulations, found clear differences in the structural dynamics of Au nanocrystal surface and bulk atoms. In particular, they found that coherent electron diffraction patterns recorded from individual nanocrystals are very sensitive to the atomic structure of nanocrystal surfaces. Obviously, the effect of surface atoms/molecules becomes relevant (i.e., appreciable at the macroscopic level) only when the number of surface atoms/molecules is not negligible compared to that of the bulk atoms/molecules. This condition occurs when crystal surface/volume ratio becomes very high, and this, in turn, happens for crystal radii falling in the nanometer range. The physical frame mentioned previously can be adopted not only for nanocrystals of metals but also for organic nanocrystals [254]. Indeed, the melting entropy of organic crystals is essentially constituted by a vibrational part, which implies that molecules in organic crystals take a similar effect of the
atoms in metallic crystals. Accordingly, for the molecular solids, the difference in the activation energy between the surface and the bulk can be explained by a difference in molecular mobility.

While the temperature/enthalpy dependence on crystal radius has been experimentally proved and modeled by many researchers [251,255], solubility dependence on crystal radius is more controversial as its experimental determination is very difficult [256]. Indeed, (1) finely divided crystals possessing lattice defects cannot be used for experimental tests as their surface characteristics can be changed by manufacturing processes [257], (2) small amounts of impurities can substantially change the solubility, and (3) polydisperse crystalline systems are affected by Ostwald ripening [258]. This phenomenon consists of larger crystal growth at the expense of smaller particles and the asymptotic reduction of solution solubility. Indeed, the dissolution of small crystals, characterized by higher solubility, renders the liquid phase oversaturated with respect to big crystals, characterized by lower solubility. Thus, part of the solute leaves the solution and provokes bigger crystal growth.

However, the possibility of increasing drug bioavailability recurring to simple physical treatments (nanonization) encouraged researchers to continue studying this problem [259–261]. In addition, the realization of nanocrystal drugs does not imply regulatory problems as FDA approval for the original drug still holds for the nanocrystal drug being its chemical composition and physical structure unaffected by the nanonization process. Finally, despite the theoretical complexity connected to the study of nanocrystal solubility increase, the realization of stable nanocrystal dispersions into a stabilizing matrix (usually a polymer) is not so difficult. Among the possible strategies adoptable at this purpose, solvent swelling [262,263], supercritical fluids [264,265], and co-grinding [266,267] can be mentioned. Solvent swelling technique is performed by letting the polymeric matrix in contact with a highly concentrated drug solution able to swell the matrix (one-stage approach). Solvent removal is achieved, for example, by means of physical treatments (natural or forced evaporation, extraction by other solvents). As, usually, organic solvents are needed to solubilize poorly water-soluble drugs (i.e., those drugs that can take the biggest advantage, in terms of bioavailability enhancement, from their nanonization), solvent removal can be a long and expensive step. Accordingly, a double-stage loading is adopted. First, the drug is solubilized in a small volume of a proper organic solvent (i.e., carbon dioxide is the most likely candidate), and then, this solution is solubilized in a large water volume (obviously, in relation to the chosen drug and matrix, the correct organic solvent must be considered, if it exists). Then matrix swelling occurs in this water–organic solvent–drug solution. In so doing, matrix swelling is favored, and solvent removal is no longer so critical as the amount of organic solvent to be removed is, usually, much less than in the one-stage approach.

Interestingly, supercritical fluids show a density approaching that of liquids (this usually implies good solubility with respect to drug or solvents used in the solvent swelling technique), and at the same time, the matrix material is characterized by low viscosity, typical of gases. Consequently, they can easily and efficiently swell the matrix, and they can be then removed by a simple pressure decrease (this provokes the transition from the supercritical condition to the gas one). Among the possible substances that can be used, carbon dioxide is the most frequently used as its critical point can be simply reached (31°C and 72 atm). When the drug shows a good solubility in the supercritical fluid, drug loading occurs by matrix swelling in the solution formed by the supercritical fluid and the drug. If, on the contrary, drug solubility in the supercritical fluid is very low, the antisolvent strategy is adopted. Accordingly, drug loading in the polymeric matrix is achieved as in the solvent swelling technique (one-stage approach). Then, the organic solvent used in the matrix swelling step is removed by putting the matrix–drug system in contact with the supercritical fluid. Obviously, the antisolvent approach works only if the organic solvent is much more soluble in the supercritical fluid than the drug.

Another approach devoted to drug loading in the polymeric matrix relies on co-grinding. This process uses the mechanical energy supplied to the drug–polymer system by the colliding grinding media. Indeed, as in the collision zones a very high temperature can be reached, the drug there present can melt and can move inside the polymeric network. Alternatively, it can be reduced to nanocrystal lying on the polymeric matrix surface [267]. The advantage of this approach consists in avoiding the use of solvents, whose elimination can be a long and an expensive step. On the contrary, this approach can be used only when the polymeric matrix is in form of small particles.

### 15.6.2.2 Mathematical Modeling

#### 15.6.2.2.1 Melting Temperature and Enthalpy Depression with Crystal Radius

Brun and coworkers [252], starting from the Laplace and Gibbs–Duhem equations, found the following relation:

\[
\int_{T_{\text{nc}}}^{T_{\text{moo}}} \frac{\Delta h_{\text{moo}}}{T} \,dT = -2 \left( \frac{\gamma_{lv}}{\rho_{s} R_{sl}} + \gamma_{lv} \left( \frac{1}{\rho_{s}} - \frac{1}{\rho_{l}} \right) \frac{1}{R_{nc}} \right) \tag{15.86}
\]

where

- \( T_{\text{moo}} \) and \( T_{\text{nc}} \) are, respectively, the melting temperature of the crystal of radius \( R_{\text{nc}} \) and of the macrocrystal (\( R_{\text{nc}} \to \infty \)),
- \( \Delta h_{\text{moo}} \) is the melting enthalpy of the crystal of radius \( R_{\text{nc}} \),
- \( \gamma_{lv} \) and \( \gamma_{sl} \) are, respectively, liquid drug–vapor and solid drug–liquid drug surface tensions,
- \( \rho_{s} \) and \( \rho_{l} \) are, respectively, solid and liquid drug density, while \( R_{s} \) and \( R_{l} \) are, respectively, the solid drug–liquid drug and the liquid drug–vapor curvature radii.
In order to render Equation 15.86 operative, it is necessary to establish a relation between \( R_{ij} (=R_{nc}) \) and \( R_{ijv} \). At this purpose, it is important to remember that in real situations, crystal melting occurs in the presence of an amorphous drug phase surrounding each nanocrystal. When, upon heating, system temperature exceeds the glass transition temperature of the amorphous drug (\( T_{gad} \)), this phase undergoes a second-order phase change from glassy to liquid. As \( T_{gad} \) is considerably smaller than nanocrystal melting temperature, whatever \( R_{nc} \), nanocrystal melting will occur in the presence of a drug liquid phase. In addition, it must be taken into consideration that also when the amorphous drug is not present, nanocrystal melting occurs by the preventive formation of a thin liquid layer surrounding the solid core [268]. Taking the melting temperature as the equilibrium temperature between the solid crystal core and the liquid overlayer of thickness \( \delta_0 \), \( R_{ij} \), and the volume of the liquid shell (\( \delta V_i \)) can be expressed in terms of \( \delta_0 \) as \( R_{ij} = R_{ijv} + \delta_0 \) and \( \delta V_i = (4/3)\pi((R_{ijv} + \delta_0)^3 - R_{ijv}^3) \). Then Equation 15.86 becomes

\[
\int_{T_{nc}}^{T_{ncf}} \frac{\Delta h_{ncf}}{T} dT = -2\left( \frac{\gamma_{lv}}{\rho_{lv}} R_{ij} + \gamma_{lv} \left( \frac{1}{\rho_{lv}} - \frac{1}{\rho_{ij}} \right) R_{ijv} + \delta_0 \right) \]  

(15.86a)

Remembering the relation existing among \( R_{ij}, R_{ijv}, \) and the nanocrystal mass fraction \( X_{ncr} \), we get

\[
X_{ncr} = \frac{V_i}{V_{ij} + \delta V_i} = \frac{(4/3)\pi R_{ijv}^3 \rho_{ij}}{(4/3)\pi R_{ijv}^3 \rho_{ij} + (4/3)\pi \rho_{ij} \left( R_{ijv}^3 - R_{ijv}^3 \right)}
\]

\[
= \frac{R_{ijv}^3 \rho_{ij}}{R_{ijv}^3 \rho_{ij} + \rho_{ij} \left( R_{ijv}^3 - R_{ijv}^3 \right)} \]  

(15.87)

Observing that for organic drugs \( \rho_{ij} \approx \rho_{lv} \), we have

\[
\delta_0 = R_{ij} \left( \frac{1}{X_{ncr}} - 1 \right) \]  

(15.88)

Obviously, while Equation 15.88 strictly holds for monodisperse nanocrystal size distribution, it holds on average for polydisperse size distribution. The combination of Equations 15.86a and 15.88 leads to our working equation

\[
\int_{T_{nc}}^{T_{ncf}} \frac{\Delta h_{ncf}}{T} dT = -\frac{2}{R_{nc}^3} \left( \frac{\gamma_{lv}}{\rho_{lv}} + \gamma_{lv} \left( \frac{1}{\rho_{lv}} - \frac{1}{\rho_{ij}} \right) X_{ncr}^{1/3} \right) \]  

(15.89)

where \( R_{ij} \) has been replaced by \( R_{nc} \). In order to get Equation 15.89 solution, the knowledge of the dependence of nanocrystal specific melting enthalpy (\( \Delta h_{ncf} \)) on nanocrystal melting temperature (\( T_{ncf} \)) and radius (\( R_{nc} \)) is needed. Among the different possibilities available in literature at this purpose, we looked at an approach independent on crystal nature (organic or inorganic), characterized by measurable parameters and leading to an analytical expression. Accordingly, the classical thermodynamic relation used by Zhang and coworkers was used [255]:

\[
\Delta h_{ncf} = \Delta h_{ncf} - \frac{3}{R_{nc}^3} \left( \frac{\gamma_{lv}}{\rho_{lv}} - \frac{\gamma_{lv}}{\rho_{ij}} \right) - \int_{T_{nc}}^{T_{ncf}} \Delta c_p dT \]  

(15.90)

where

\[
\Delta h_{ncf} \] is the specific melting enthalpy referred to the infinite radius drug crystal

\[
\Delta c_p \] is the difference between the liquid and the solid drug specific heat capacity at constant pressure

As \( \Delta c_p \) is almost temperature invariant, the third term on the right-hand side of Equation 15.90 can be approximated by \( \Delta c_p (T_{ncf} - T_{nc}) \). On the contrary, the radius dependence of \( \gamma_{lv}, \gamma_{lv}, \) and \( T_{nc} \) must be accounted for, and the following well-known equation [269–272] was considered:

\[
\frac{\gamma_{lv}}{\gamma_{lv}} = (1 + 2\delta/\rho_{nc})^{-1} \]  

(15.91)

where \( \gamma_{lv} \) and \( \gamma_{lv} \) are, respectively, the surface tension competing to a flat surface (infinite curvature radius) and a surface of curvature radius \( R_{nc} \). i and j indicate, respectively, the solid, liquid, or vapor phase, while \( \delta \) is the Tolman length whose order of magnitude should correspond to the effective molecular diameter \( \alpha \) [270] and it is usually assumed to be \( \alpha/3 \) [273]. Equation 15.91 predicts that the surface tension approaches to zero for vanishing values of \( R_{nc} \).

The determination of \( \Delta h_{ncf}(R_{nc}), T_{ncf}(R_{nc}), \) and \( X_{ncr} \) can be achieved by means of the numerical, simultaneous solution of Equations 15.89 and 15.90 [267]. As in real situations what we know is the differential scanning calorimeter (DSC) pattern referring to drug nanocrystal melting while \( X_{ncr} \) is unknown, Equation 15.89 and 15.90 solution requires an iterative solving procedure. Accordingly, a first attempt value for \( X_{ncr} \) is fixed, and then, \( X_{ncr} \) is recalculated according to

\[
X_{ncr} = \frac{\Delta h_{lg}(T_{ncf}, \omega_{lg})}{\Delta h_{ncf}(T_{ncf}, \omega_{lg}) - \omega_{l} (\Delta h_{lg} + \Delta h_{fy})} \]  

(15.92)

where \( \Delta h_{lg} \) is the experimentally determined melting enthalpy referred to the system unit mass (polymer plus drug that underwent the nanization process) and evaluated at \( T_{ncf} \) (as the polymer is amorphous, \( \Delta h_{lg} \) is only due to drug melting), \( \omega_{lg} \) is the drug mass fraction characterizing the drug polymer system, \( \Delta h_{mix} \) is the experimentally known
drug melting enthalpy evaluated at \( T_{\text{m}} \) and \( \omega_0 \), and referring to the unit mass of the drug–polymer system obtained by the simple physical mixing of drug and polymer (in this system, the drug does not undergo the nanonization process), while \( \Delta h_r \) and \( \Delta h_T \) are the specific enthalpy corrections (referred to pure drug unit mass) representing the nanocrystal melting enthalpy reduction due to nanocrystal radius reduction and melting temperature reduction (see, respectively, the second and third terms in the right-hand side of Equation 15.90). \( \Delta h_r \) and \( \Delta h_T \) are determined in the simultaneous solution of Equations 15.89 and 15.90. If the relative difference (\( R_d \)) between \( X_{\text{ncr}} \) value calculated according to Equation 15.92 and that initially assumed as first attempt is less than a fixed threshold (\( \text{Tol} \)), the iterative procedure is stopped and Equations 15.89 through 15.92 solution provides \( \Delta h_{mr}(R^{\text{nc}}) \), \( T_{mr}(R^{\text{nc}}) \), and \( X_{ncr} \). On the contrary, the procedure is repeated assuming as new value for \( X_{ncr} \) the following one:

\[
X_{ncr} = X_{ncr}^{old}(1 - \lambda) + \lambda X_{ncr}^{new} \tag{15.93}
\]

where \( \lambda \) is the relaxation parameter ranging between 0 and 1, \( X_{ncr}^{old} \) and \( X_{ncr}^{new} \) represent, respectively, the \( X_{ncr} \) value assumed at the beginning of the \( i \)th iteration loop and that recalculated according to Equation 15.92 at the end of the \( i \)th iteration loop.

The procedure is repeated up to \( R_d < \text{Tol} \). In case the drug nanonization process did not affect all the drug mass, the mass fraction (\( X_a \)) of the remaining original macrocrystals can be evaluated by

\[
X_a = 1 - X_l - X_{ncr} \tag{15.95}
\]

Once \( \Delta h_{mr}(R^{\text{nc}}) \), \( T_{mr}(R^{\text{nc}}) \), and \( X_{ncr} \) are known, it is possible evaluating nanocrystal size distribution. The starting point is the relation among the volume \( dV_a \) occupied by nanocrystals whose radius lies in the range \( R^{\text{nc}} - (R^{\text{nc}} + dR^{\text{nc}}) \) and their specific melting enthalpy \( (d/kg) \) \( \Delta h_{mr} \), melting enthalpy \( (J) \) \( \Delta H_{mr} \), and density \( \rho \):

\[
dV_a = \frac{d(\Delta H_{mr})}{\Delta h_{mr} \rho} \tag{15.96}
\]

From Equation 15.96, we have

\[
\frac{dV_a}{dR^{\text{nc}}} = \frac{d\Delta H_{mr}}{dR^{\text{nc}}} \frac{1}{\Delta h_{mr} \rho} = \frac{\frac{d\Delta H_{mr}}{dT_{mr}}}{dR^{\text{nc}}} \frac{1}{\Delta h_{mr} \rho} = \frac{\frac{\frac{d\Delta H_{mr}}{dT_{mr}}}{dT_{mr}}}{\Delta h_{mr} \rho} = \frac{\frac{\frac{d\Delta H_{mr}}{dT_{mr}}}{dT_{mr}}}{\Delta h_{mr} \rho} \frac{1}{\nu} \tag{15.97}
\]

where

\[
\begin{align*}
\nu & \text{ is the DSC heating rate } (\text{C/min}) \\
Q & \text{ is the heat flow registered by DSC (mW)}
\end{align*}
\]

Equation 15.97 allows the determination of the nanocrystal differential volume distribution \( (dV_a/dR^{\text{nc}}) \) as \( Q, \nu, \Delta h_{mr}(R^{\text{nc}}) \) are known, and the function \( dV_a/dR^{\text{nc}} \) can be numerically determined on the basis of the numerical solution of Equations 15.90 and 15.91. Accordingly, the nanocrystal differential volume distribution is given by

\[
f(R^{\text{nc}}) = \frac{dV_a}{dR^{\text{nc}}} \int_{R^{\text{min}}}^{R^{\text{max}}} \frac{dV_a}{dR^{\text{nc}}} dR^{\text{nc}} \tag{15.98}
\]

where \( R^{\text{nc}} \) and \( R^{\text{min}} \) represent, respectively, the maximum and minimum value assumed by \( R^{\text{nc}} \) while \( f \) is nothing more than the probability of finding a nanocrystal of radius \( R^{\text{nc}} \).

15.6.2.2 Solubility Enhancement with Decreasing Crystal Radius

In order to evaluate the nanocrystal solubility dependence on \( R^{\text{nc}} \), the classical thermodynamic approach ruling the equilibrium between a liquid phase (water or a physiological medium, i.e., our solvent) and a nanocrystalline solid phase (drug) was used [274]. Assuming that only the drug partitions between the two phases (this means that the solvent does not go inside the drug), the equilibrium condition requires that the drug fugacity in the solid phase \( f_d^s \) equates the drug fugacity in the solvent \( f_d^l \). By definition, we have

\[
f_d^l = \gamma_d X_a f_d^l = \gamma_d f_d = f_d \tag{15.99}
\]

where

\[
\gamma_d \text{ and } X_a \text{ are, respectively, the drug activity coefficient and solubility (molar fraction) in the solvent}
\]

\( f_d^l \) is the drug fugacity in the reference state, while \( f_d^s \) is the drug fugacity in the solid state.

Accordingly, drug solubility in the solvent will be given by

\[
X_a = f_d^s \frac{1}{\gamma_d} \tag{15.100}
\]
Assuming \( f_d \) as the fugacity of pure drug in the state of undercooled liquid at the system temperature \( T \) and pressure \( P \), the ratio \( f_d / f_d^0 \) can be evaluated according to

\[
\Delta G_{4i} = RT \ln \left( \frac{f_d}{f_d^0} \right) \tag{15.101}
\]

where

- \( R \) is the universal gas constant
- \( \Delta G_{4i} \) represents the variation of the specific Gibbs free energy between the state of undercooled liquid drug (state 4) and solid (nanocrystalline) drug (state 1)

\( \Delta G_{4i} \) can be conveniently evaluated according to a thermodynamic cycle where the solid nanocrystals at \( T \) and \( P \) represent state 1; state 2 is given by nanocrystals heated, at constant pressure \( P \), up to their melting temperature \( T_{mr} \); state 3 represents the completely melted nanocrystals at \( T_{mr} \) and \( P \); and state 4 is achieved by cooling at constant pressure \( P \) up to \( T \), the liquid drug (undercooled liquid). Accordingly, it follows

\[
\Delta G_{4i} = \Delta H_{4i} - T \Delta S_{4i} = \Delta H_{21} + \Delta H_{32} + \Delta H_{43} - T \left( \Delta S_{21} + \Delta S_{32} + \Delta S_{43} \right) \tag{15.102}
\]

where \( \Delta H_{ij} \) and \( \Delta S_{ij} \) are, respectively, the variation of the specific enthalpy and entropy between state \( j \) and \( i \). In details, we have

\[
\Delta H_{21} = \int_{T_{mr}}^{T} c_p^s dT \approx c_p^s(T_{mr} - T),
\]

\[
\Delta S_{21} = \int_{T_{mr}}^{T} c_p^s \frac{dT}{T} \approx c_p^s \ln \left( \frac{T_{mr}}{T} \right), \quad \text{[as } dP = 0 \text{]} \tag{15.103}
\]

\[
\Delta H_{32} = \Delta h_{mr}, \quad \Delta S_{32} = \Delta s_{mr} \left( \text{as } \Delta g_{mr} = \Delta h_{mr} - \Delta s_{mr} = 0 \right) \tag{15.104}
\]

\[
\Delta H_{43} = \int_{T_{mr}}^{T} c_p^l dT \approx c_p^l(T - T_{mr}),
\]

\[
\Delta S_{43} = \int_{T_{mr}}^{T} c_p^l \frac{dT}{T} \approx c_p^l \ln \left( \frac{T}{T_{mr}} \right), \quad \text{[as } dP = 0 \text{]} \tag{15.105}
\]

where \( c_p^s \) and \( c_p^l \) are, respectively, the solid (drug) and liquid (drug) specific heat at constant pressure, while \( \Delta g_{mr} \) and \( \Delta s_{mr} \) are, respectively, the specific nanocrystal melting Gibbs free energy and entropy. Upon rearrangement of Equations 15.100 through 15.105, drug solubility can be expressed as a function of determinable parameters:

\[
X_d = \frac{1}{Y_d} \left( \frac{T}{T_{mr}} \right)^{X_{ncr}/R} \exp \left\{ - \left[ \frac{\Delta h_{mr}}{RT} + \frac{\Delta c_p}{R} \left( 1 - \frac{T}{T_{mr}} \right) \right] \right\} \tag{15.106}
\]

where \( \Delta c_p = c_p^s - c_p^l \). On the basis of Equation 15.106, it follows that drug solubility expressed in terms of mass/volume is given by

\[
C_{sm} = \frac{X_d}{1 - X_d} \frac{M_d}{M_s} \rho_{sol} \tag{15.107}
\]

where \( M_d \) and \( M_s \) are, respectively, drug and solvent molecular weight, while \( \rho_{sol} \) is the solvent density.

### 15.6.2.3 Bioavailability Improvement

Equation 15.106 clearly shows that drug solubility in the solid phase depends on the melting properties of nanocrystals \( T_{mr} \) and \( \Delta h_{mr} \) that, in turn, depend on the nanocrystal radius \( R_{nc} \) as discussed in Section 15.6.2.2.1. Figure 15.25 reports the dependence of \( T_{mr} \) and \( \Delta h_{mr} \) on \( R_{nc} \) for two different values of \( X_{ncr} \) in the case of nimesulide, a poorly water-soluble drug belonging to the class of the nonsteroidal anti-inflammatory drugs. This simulation, numerical solution of Equations 15.90 and 15.91, was performed knowing that, in the case of nimesulide, the Tolman length is \( \delta = 0.238 \) nm; the melting temperature is \( T_{mr} = 148.7 \text{°C} \); the melting enthalpy is \( \Delta h_{mr} = 109,000 \text{ J/kg} \); the difference between the solid and liquid drug specific heat at constant pressure is \( \Delta c_p = 333 \text{ J/kg°C} \); the solid and liquid drug density is, respectively, \( \rho_s = 1,490 \text{ kg/m}^3 \) and \( \rho_l = 1,343 \text{ kg/m}^3 \); and the solid–liquid, solid–vapor, and liquid–vapor surface tensions are, respectively, \( \gamma_{dl} = 13.3 \times 10^{-3} \text{ J/m}^2 \), \( \gamma_{sv} = 57.6 \times 10^{-3} \text{ J/m}^2 \), and \( \gamma_{lv} = 70.6 \times 10^{-3} \text{ J/m}^2 \).

**FIGURE 15.25** Decrease of the melting temperature (\( T_{mr} \), thin lines) and enthalpy (\( \Delta h_{mr} \), thick lines) with nanocrystal radius (\( R_{nc} \)) for two different values of the nanocrystal mass fraction \( X_{ncr} \).
and $\gamma_{nc} = 44.3 \times 10^{-3}$ J/m$^2$ [267]. Figure 15.25 clearly shows the reduction of both $T_{nc}$ and $\Delta h_{nc}$ with $R_{nc}$. It can be noted that this reduction is more pronounced for the lowest value of the nanocrystal mass fractions ($X_{ncr} = 0.01$). This means that the increasing presence of the amorphous drug phase favors the nanocrystal melting process. In the case of $X_{ncr}$ values lying in between the two chosen in Figure 15.26, the corresponding trends of $T_{nc}$ and $\Delta h_{nc}$ proportionally collocate among those pertaining to $X_{ncr} = 0.01$ and 0.99. Based on the results of Figure 15.25, Figure 15.26 reports the corresponding solubility increase with $R_{nc}$ supposing that the nimesulide activity coefficient does not depend on drug concentration and it is equal to 115.572 [267]. The solubility increase is expressed as the ratio between the nanocrystal solubility $C_{snc}$ and the solubility $C_s (= 9 \mu g/mL$; water, 37°C), pertaining to the infinitely large crystal (i.e., the commonly defined drug solubility). It can be seen that, depending on the $X_{ncr}$ value, $C_{snc}$ can be up to five to nine times $C_s$. It is also interesting to note that as $T_{nc}$ and $\Delta h_{nc}$ depend on $X_{ncr}$, also $C_{snc}$ depends on $X_{ncr}$. This means that the higher the amount of amorphous drug, the higher the nanocrystal drug solubility. In other words, the solubility of nanocrystals is affected also by the surrounding environment, here intended as the relative abundance of amorphous drug. This descends from the thermodynamic cycle used for the estimation of $\Delta G_{snc}$ (variation of the specific Gibbs free energy between the state of undercooled liquid drug and solid [nanocrystalline] drug).

Obviously, in real polymer–drug systems, the frame is complicated by the polydispersity of nanocrystal size distribution (as shown by Equations 15.96 through 15.98) that implies the existence of nanocrystals characterized by different solubility. However, as a first approximation, the solubility of a polydisperse nanocrystal ensemble can be identified with that competing to the nanocrystal characterized by the radius $R_{nc}^m$ having the highest probability of being found in the nanocrystal size distribution, that is the radius corresponding to the peak of the probability function $f$ (see Equation 15.98).

The possibility of increasing drug solubility recurring to a simple physical process (nanonization) plays a paramount role in bioavailability enhancement. Indeed, bioavailability, defined as the rate and extent to which the active drug is absorbed from a pharmaceutical form and becomes available at the site of drug action [123], depends on several factors, among which drug solubility in an aqueous environment and drug permeability through lipophilic membranes play the role of key parameters [275]. As drug permeability cannot be easily and safely improved, the enhancement of drug solubility remains the only tool at our disposal for increasing drug bioavailability. This is the reason why the drug nanonization approach plays a paramount importance in the pharmaceutical field.

The in vitro and in vivo effect of this strategy can be witnessed by many experimental results. For example, in vitro release of TEM (temazepam, benzodiazepine derived; sedative and hypnotic) and MAP (medroxyprogesterone acetate; antitumoral) proved the considerable effect of the nanonization process [263]. In addition, the nanonization approach proved to be very reliable and promising in the case of other drugs such as griseofulvin (antifungal) [276], phenytoin (anti-spasmodyic) [277], nifdefpine (anti-hypertensive) [278], MPA (methylhydroxyprogesterone acetate, antitumoral) [279], and anti-inflammatory drugs [280]. In these examples, in vivo tests showed that the nanonization process is reflected in an increase of the oral area under the curve (AUC: it is the area generated by the time course of the drug concentration in the blood after drug oral administration), with respect to that competing to the drug that is not nanosized, spanning from 1.1 to 3. This is, of course, very important as drug bioavailability is directly proportional to the oral AUC.

Finally, we would like to conclude this paragraph mentioning another aspect that is strictly correlated with drug status in the delivery system. At this purpose, recently, Hadgraft, discussing the importance of excipients in skin delivery [283], reported on the failure of transdermal patches containing fentanyl, a pain-relieving drug. The rapid diffusion of the solvent (ethanol) out of the matrix patch led to fentanyl crystallization on skin surface and in the patch matrix, and this, in turn, provoked drug release stopping. Accordingly, the importance of knowing the drug status (macro- or nanocrystals or amorphous) inside the delivery system is clear.

### 15.7 CONCLUSIONS

This chapter, aimed to illustrate and to discuss membrane applications in the delivery field devoting particular care to the mechanisms ruling mass transport, makes clear that membranes often play a key role as they are very versatile. Indeed, while they can be used to modulate drug mass flux in order to guarantee the desired release kinetics, they can also act as barriers separating an external environment from an internal environment as shown through this chapter. Obviously, due to the great variety of applications, it was not
possible to consider all of them, but we believe that the most significant have been shown. In addition, some of them, for the sake of brevity, could not be discussed. In particular, we refer to the wide field of living cell encapsulation techniques used in tissue engineering [12,282]. In this case, interestingly, membranes are called to contemporaneously act as barrier and mass transport modulators. Indeed, they must protect living cells hosted in the microcapsule from the immune response of the hosting body where they are implanted to perform their action (e.g., insulin release in diabetic patients). Accordingly, membrane must be impermeable to immunoglobulins, big molecules devoted to the destruction of foreign bodies. Contemporaneously, however, they must allow nutrients (Na\(^+\), K\(^+\), oxygen, and glucose) permeation to feed encapsulated cells. Clearly, this is just a further example of the complexity of membrane actions, and it underlines that a proper membrane designing is needed. A possible tool to match this goal is represented by mathematical modeling, and this is the reason why the initial part of this chapter is devoted to describe release mechanisms, fundamental bases for getting a reliable mathematical model.

REFERENCES


Membranes in Drug Delivery


Membranes in Drug Delivery


