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Choosing a Membrane For Use with PermeGear Cells

The first consideration in choosing a membrane to use with PermeGear cells is to identify or reference the objective of the experiment or studies to be carried out. Characterizing the membrane itself may be the goal for evaluating and selecting prospective components for medical devices. In these cases, membranes are usually solid and homogeneous, but could also be porous, heterogeneous, and/or layered to achieve a desired rate control for optimizing the release profile of an active pharmaceutical ingredient (API) from a medical device or pharmaceutical dosage form. To characterize components of medical and pharmaceutical devices, diffusion coefficients of the component materials can be calculated with PermeGear cells by determining permeation rates through defined thicknesses of a material. In addition to characterizing device component permeability, some polymer membranes can be used as surrogates for viable tissues. Evaluating the permeability of polymer membranes is required when they are proposed as substitutes for viable tissue.

Diffusion cell membranes are valuable aids in formulating topical and transdermal pharmaceuticals. Product development often requires measuring diffusion parameters either between immiscible phases, through continuous or heterogeneous phases, into and/or through barrier membranes, or some combination of each these phenomena. The results of these preliminary studies facilitate experiments to optimize the final product. These experiments usually fall into one of two categories, permeation testing or release testing. Release testing determines the time profile of the API diffusing out of one medium--a donor solution or formulation, also called a vehicle--into a "perfect" sink which is generally a medium where the solubility of the API in the receptor medium does not hinder the transfer of the API out of its vehicle. Likewise, the ideal membrane provides no resistance to the release of the API from its formulation. A porous membrane, such as a dialysis membrane or membrane filter, is an appropriate choice for release testing or interphase transfer experiments. In contrast, permeation testing also involves the permeability of a membrane to an API. In that case, both the membrane and the formulation determine the rate an API will diffuse from its vehicle into the receptor chamber.

The membrane of choice for permeation testing is the biological tissue for which the device or dosage form is to be applied to. Thus for transdermal patches and most topical pharmaceuticals, excised human skin is recommended. Intestinal membranes and stomach lining are harvested for studying absorption of oral drugs. PermeGear even has cells specially designed for studying permeation through corneal tissue. Excised human skin can be procured from burn banks, tissue supply houses, and hospitals following autopsy or surgical procedures. Animal models such as hairless mouse, hairless rat, guinea pig, and pig skin are frequently used as substitutes for human skin. Synthetic polymers are used in place of human skin for permeation testing, as well. When using substitutes instead of the target viable tissue, correlating the results with those obtained from preliminary or concurrent experiments on the harvested tissue is recommended. Strat-M is one commercially available synthetic membrane that has been developed to emulate the two-layer characteristics of human epidermis. A short and descriptive video and correlation data[1] are available. Table I contains a partial list of polymer films which may be useful for characterizing device components or as substitutes for viable tissues.

Membranes developed for filtering liquids (membrane filters) are most popular for studying the release of an API from its formulation. In vitro release testing (IVRT) is required for batch to batch quality control of topical pharmaceutical products. Commercially available membrane filters differ in diameter, pore size, thickness, chemical composition, and type of porosity. Table II lists most common membrane filters with their corresponding membrane characteristics and where they can be purchased.

Most membrane filters are circular and commonly available in 13, 25, and 47 mm diameters. Some filters are available as sheets. Dialysis membranes can also be used for IVRT experiments and are available as sheets or tubes. Although membranes are easily trimmed to suit one's cell dimensions, a 25 mm diameter filter is most appropriate to fit the 15 mm PermeGear cells and 47 mm diameter filters are well-suited for 25 mm cells. In-Line cells are square and 25mm filters must be trimmed on each side to fit.

Membrane filters used for IVRT should provide minimal resistance to the API diffusing out of its formulation while completely retaining all other components of the formulation. Although this is virtually impossible in practice--choice of pore size, thickness, and composition should all be considered in making an optimal membrane choice.

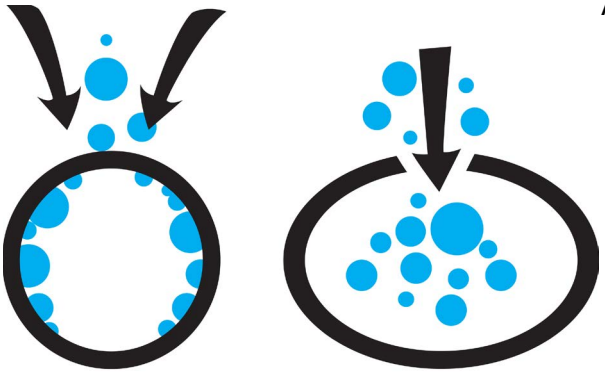
Hatanaka, et al[2]. derived an equation for predicting steady-state diffusion through a membrane with multiple pathways, which embodies most of the factors involving permeation through membranes. The steady-state rate of diffusion, or flux, is given by $J = DKCp/th$ where D represents a coefficient of molecular diffusion through the liquid in the pores of the membrane, K is a partition coefficient between the membrane and the vehicle, and C is the concentration of the diffusant in its vehicle. Porosity, tortuosity, and thickness are represented by p, t, and h, respectively.

In the absence of any absorption and adsorption--K, D, and C typically involve only the properties of a diffusing molecule or experimental factors other than the membrane. For pore sizes greater than the API, only the porosity, tortuosity, and thickness of a membrane should affect the permeation rate. In a paper comparing a dozen porous membranes, the authors found evidence that thin membranes with high porosity and low tortuosity make the best choice for IVRT membranes[3] . Unfortunately, porosity and tortuosity data are not available for most membranes.

A membrane's pore size should be large enough that an API will easily diffuse through, but not other formulation components. With dialysis membranes, the largest molecules that can pass through the membrane determines the pore size. The corresponding molecular weight cut-off (MWCO) can be used as a rule of thumb in estimating the likelihood of any hindrance to diffusion through a dialysis membrane. Some common dialysis membranes, with their properties and suppliers, are shown in Table III. See Appendix A for more information on pore size and other membrane characterization measurements such as porosity and tortuosity.

In general, the thicker a membrane is, the slower an API will diffuse through since permeability is inversely proportional to membrane thickness. This is useful for optimizing a rate-limiting delivery device or developing a polymer film as a model for a bio-membrane substitute. However, IVRT membranes should be as thin as possible. Because thinner membranes can be more delicate or too flexible, some composite filters, such as Fluoropore[4], have sturdier support layers. Non-woven supports (as opposed to nets or screens) are bonded to the filter material by spraying melted polymer beads through nozzle guns to produce a random pattern, presumably adding physical strength without compromising any filtration properties.

The chemical composition of membranes affects the degree to which proteins and other molecules should be bound to or absorbed by them. Appendix B contains supplemental information on absorption, adsorption, and protein binding. Some polymer membranes contain ionizable groups which may provide functional value for filtration of charged molecules, but are potentially undesirable for IVRT where the membrane should be as inert as possible.



Adsorption to or absorption into the polymer matrix is an important consideration when choosing a membrane filter for IVRT experiments. Functional groups on membrane polymers affect the degree to which adsorption to the membrane can occur. Hydrophilicity and lipophilicity are rough indications of the solubility of APIs in water or oil media, respectively. Similarly, an API that is hydrophilic will have affinity to a hydrophilic polymer and a lipophilic API will have affinity for a lipophilic polymer. However, the terminology describing the hydrophobicity or hydrophilicy of membrane filters can be misleading. Hydrophilic filters are designed for fast wetting so that filtering aqueous solutions results in faster flow rates[5]. But this has little to do with the degree to which a lipophilic molecule may adhere to the membrane or be absorbed by it. When there is any concern over the possibility that an API will adsorb onto or be absorbed by a membrane, compatibility testing is recommended. At a minimum compatibility data should be consulted, if available. For example, Cole Parmer's compatibility tool[6] rates polypropylene compatibility with naphthalene as good, whereas silicone is not recommended for use with naphthalene. Several compatibility resources are listed in Appendix C.

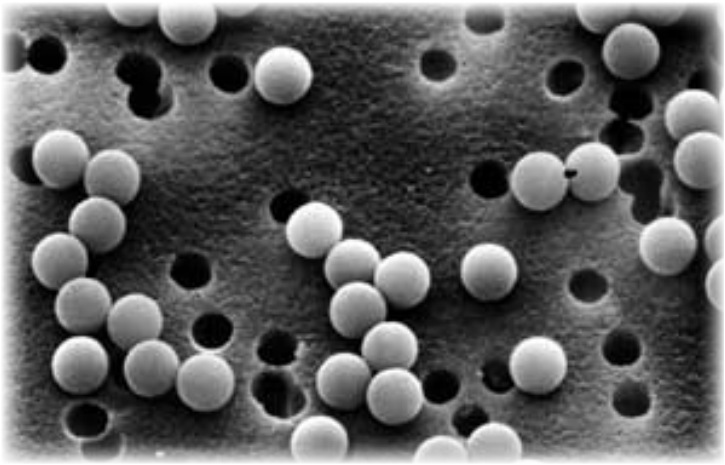
To test compatibility, expose the API, its formulation components, and the receptor fluid to a membrane and observe any adverse visual effects, like excessive shrinking or swelling. To judge adsorption and absorption, membranes should be immersed in low enough concentrations that disappearance of the API can be quantitated. Theoretically, the membrane itself may cause interference with sample analysis due to extractables produced during manufacture.

Membrane extractables[7]--artifacts present in synthetic membranes introduced during the manufacturing or packaging process—may interfere with chromatographic analysis by co-eluting with an API or introducing extraneous peaks. An artifact may be a component of the membrane or a particle trapped in the pore structure. Components of a drug formulation or a receptor fluid may trigger the release of extractables during a diffusion experiment. Chemical compatibility affects how significant the resulting sample contamination can be. Membranes should be exposed to formulations and receptor fluids preliminarily to assess the possibility of extractables appearing in diffusion samples. More information on extractables can be found on pages 18-19 of a technical paper on HPLC filtration[8].

Appendix A

Membrane pore sizes are given in micrometers (µm) and represent an approximate diameter of channels or pores through which a molecule or particle might diffuse through. Thus moieties larger than the pore size will be retained and those smaller than the pore size will be able to pass through. Most commercial membrane filters are fibrous and pore size is somewhat nominal. Some membranes have a very narrow pore size distribution and thus a sharp molecular mass cut-off. Others have a wider pore size distribution and therefore a more diffuse cut-off. More uniform pores exist in membranes made with ion beams from accelerators[9], such as the track-etched membranes. These have a top to bottom hole through the membrane.

Pore size can be determined by scanning electron microscopy, capillary flow porometry, or filtering particles of defined size to determine the minimum size retained. With dialysis and ultrafiltration, filter pore size is too small to be meaningful. These membranes are rated according to their MWCO or nominal molecular weight limit (NMWL). This is not a sharp cutoff. For example, a membrane rated at 30,000 will exclude a test protein with a molecular weight of 30,000 Daltons. Ninety percent of that test protein will be retained on the upstream side and 10% will pass through into the filtrate, resulting in concentration of the protein[10].



Although pore size ratings vary from manufacturer to manufacturer and from product to product, these differences are not likely to be significant for release testing. Unless there is a major difference between the API or CoI and all other formulation components, pore size will not be able to retain the components exclusively. The more important considerations are porosity, tortuosity, thickness, and absorption or adsorption. Tortuosity is another factor that can influence diffusion through a membrane, and the release rate of an API from its formulation. Tortuosity increases the path length through which a molecule must diffuse as it passes through the membrane. Therefore, with all other factors the same, release rates from the more tortuous membranes should be slower. Tortuosity should be least for track-etched membranes which have cylindrical straight-through pores. Greater tortuosity should favor the release of smaller molecules from a formulation relative to other components, because the diffusion rate will be faster for smaller molecules than for larger ones.

Although porosity and tortuosity values for membranes are not usually available, bulk air and solvent flow rates are commonly provided in the specifications for any membrane filter. Possibly the flow rate may be an indication of the combined effects of porosity and tortuosity. For membranes rated with equal pore sizes, the membrane with the faster flow rate will probably be the one with greater porosity and/or least tortuosity.

Appendix B

Adsorption is where molecules adhere to the surface of polymer matrix, whereas absorption involves molecular penetration into the polymer itself. Adsorption involves the affinity of permeant to functional groups on the polymer. Protein binding is generally all adsorption, especially if the protein is large and penetration into the bulk of the membrane is negligible. Membranes with high porosity (about 80%) provide high surface area and more likely to be susceptible to adsorption or binding[11]. Small molecules are more likely to be absorbed by the membrane. The degree of absorption depends not only on the solubility of a permeant in the polymer, but its tendency to remain in the formulation or receptor solution. Therefore a molecule with a small oil/water partition coefficient in an aqueous solution would be less likely to be absorbed by a polymer membrane filter than a more lipophilic molecule. Solubility and partition coefficient data may aid in the prediction of the compatibility of compounds with prospective polymer membranes, although a final membrane choice is best determined by experiment.

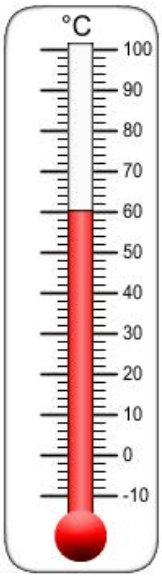
Small molecules may also adsorb to a membrane. Differentiating between adsorption and absorption can be accomplished with experiments by varying polymer dimensions and permeant concentrations.

Appendix C

The main manufacturers of membrane filters all have charts predicting the compatibility of their filters with various solvents. These compatibility references are of questionable value, because the compatibility test conditions may not apply to the conditions used in actual diffusion experiments. For example, a compound indicated as incompatible when exposed to the membrane in pure form may have little effect at the concentration present as a component of a formulation. On the other hand, a small concentration of a compound in a formulation may be absorbed by a membrane, cause it to swell, and subsequently affect the release rate of the API in the formulation.

EMD Millipore's compatibility guide[12] contains the following pertinent caveats:

1. **These recommendations assume pure solutions at room temperature and pressure without applied stresses. Time of exposure is not considered. These are critical assumptions as polymer properties are strongly affected by environmental conditions, time, the presence of external stress and the presence of additives.** It is not safe to assume that property changes are linearly related to changing temperature. A 10°C increase in temperature, for example, may place the test conditions closer to the glass transition of the polymer, thus allowing greater penetration of solvent molecules. This has a plasticizing effect, further lowering the glass transition and resulting in a modulus drop of up to three orders of magnitude. The glass transition of nylons, for example, has been shown to range from below -50 °C to +70 °C depending upon their moisture content.



2. **These recommendations assume that each polymer category has a uniform chemistry, molecular weight distribution and thermomechanical history. This assumption will never be true and, in some cases, variation has a distinct influence on compatibility.** For example, solvent compatibility of cellulose esters is strongly dependent upon their degree of substitution (acetylation/nitration). Crystalline morphology and degree of crystallinity influences compatibility of semi-crystalline polymers and can vary significantly. Polyethyleneterephthalate, for example, can be quenched to obtained samples with almost no crystallinity

or annealed to obtain samples with >50% crystallinity. The response time of these two polyesters, although chemically identical, will be quite different. The effect of molecular weight distribution and degree of branching on solvent compatibility can be seen by comparing the solvent compatibility of LDPE, LLDPE, HDPE and UPE. Such specific information concerning polymers evaluated does not accompany published compatibility tables.

3. The definition of solvent compatibility for EMD Millipore products differs from that used in determining the ratings given in published compatibility tables. **Such tables are generally concerned with chemical attack and significant losses in strength and/or dimensional changes.** A top designation, for example, might be designated for solvent-polymer combinations with <10% swelling, which is high. Other compatibility tables may make recommendations based upon dimensional change as a function of time. This is difficult to relate to a membrane that may respond almost immediately to immersion in solvent. In addition, solvent-membrane compatibility requires additional consideration of filtration-specific factors. **None of these published compatibility guides, for example, monitors the solvent's ability to wet a membrane or increase extractables.**

Pall's chemical compatibility guide[13] lists HPLC solvents and provides recommendations on the resistance to solvent flow or bubble point which usually means a change in pore size. In some cases, a limited resistance or not resistant rating applies to the housing containing the filter membrane, yet the membrane polymer might be perfectly compatible when used alone in a release experiment.

GE Healthcare Life Sciences has a similar table of solvents vs. their compatibility with all of their Whatman membrane filters[14]. Another compatibility chart has data for Nylon, PTFE, PVDF, and Regenerated Cellulose membranes[15].

Cole Parmer's compatibility tool is an interactive one where you can choose from a list of solvents or compounds and another list of materials, such as polymers, to see if they are compatible. The ratings go from excellent compatibility to not recommended for any use.

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2. https://www.ncbi.nlm.nih.gov/pubmed/2092945

3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3986717/#B32-pharmaceutics-02-00209

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5. https://www.emdmillipore.com/US/en/life-science-research/chromatography-sample-preparation/membrane-learning-center/Wettability-Characterization/lp2b.qB.f7IAAAFM20p88eJt,nav

6. https://www.coleparmer.com/chemical-resistance

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14. http://www.lifescience.ca/data/catalogue/35~v~filtration_products_information.pdf

15. https://www.coleparmer.com/chemical-resistance