

특별강연 I

Enantiospecific separation in biphasic Membrane Reactors

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Membrane reactors are systems which combine a chemical reactor with a membrane separation process allowing to carry out simultaneously conversion and product separation. The catalyst can be immobilized on the membrane or simply compartmentalized in a reaction space by the membrane.

Membrane reactors are today investigated to produce optically pure isomers and/or resolve racemic mixture of enantiomers. The interest towards these systems is due to the increasing demand of enantiomerically pure compounds to be used in the pharmaceutical, food, and agrochemical industries. In fact, enantiomers can have different biological activities, which often influence the efficacy or toxicity of the compound.

On the basis of current literature there are basically two schemes on the use of membrane technology to produce enantiomers. In one case, the membrane itself is intrinsically enantioselective: the membrane is the chiral system which selectively separates the wanted isomer on the basis of its conformation. In the other, a kinetic resolution using an enantiospecific biocatalyst is combined with a membrane separation process; the membrane separates the product from the substrate on the basis of their relative chemical properties (i.e. solubility). This kind of configuration is widely used to carry out kinetic resolutions of low water soluble substrates in biphasic membrane reactors [Giorno, 1995, 1997; Lopez, 1997].

These are systems where enzyme-loaded membranes promote reactions between two separate phases thanks to the properties of enzymes, such as lipases, to catalyse reactions at the organic/aqueous interface; the two phases are maintained in contact and separated at the membrane level by operating at appropriate transmembrane pressure. A schematic representation of biphasic membrane reactor is shown in figure 1, while an example of enantiospecific reaction and product separation carried out with these systems is reported in figure 2.

In our laboratories, biphasic membrane reactors have been studied to convert the racemic cyanomethylester of 2-(4-isobutylphenyl)propionic acid into the corresponding S-acid. Triglycerides from olive oil have been also used as a model system to study the properties of the immobilized lipase.

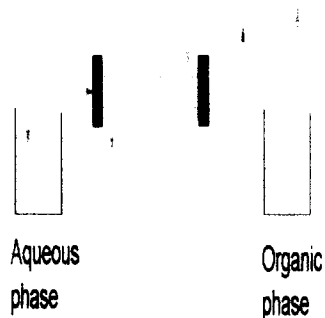


Fig. 1

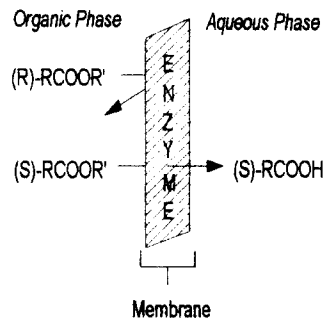


Fig. 2

Experimental studies have been carried out in order to determine the influence of operating conditions on enzyme kinetics and transport properties through the membrane system. Lipase (from *C. rugosa*) was entrapped within the spongy layer of asymmetric membranes made of polyamide. The organic phase was recirculated along the shell side and the aqueous phase along the lumen side of capillary membrane modules.

The biphasic system was characterized by studying the influence of pH, temperature and substrate concentration. In general, optimal pH and temperature values do not change very much between free and immobilized lipase (unless enzyme is immobilized by chemical bounds). These values can change if the enzyme is used with different substrates or in different buffer solutions. For example, the optimal temperature value for free and immobilized lipase is 40 °C when using olive oil as substrate, while it resulted 28-30 °C when using the cyanomethyl ester of arylpropionic acid (CNE) as substrate.

Substrate viscosity influences the performance of the system by affecting mass transfer across the membrane up to the enzyme. Studies carried out with low-water soluble substrates having different viscosity have evidenced that apparent reaction rate for enzyme loaded-systems is higher for substrates with lower viscosity.

The effects of fluid dynamics parameters, such as axial flow rate of organic and aqueous phase, transmembrane pressure, flow regime, were also investigated. The flow rate of organic phase (which contains the

substrate) strongly influences the reactor performance by affecting the mass transport coefficient. The observed reaction rate as a function of flow rate using olive oil as substrate decreases with increasing the flow rate, similar behavior is obtained using CNE as substrate, although the effect is less negative with respect to olive oil. This behaviour could be due to the fact that, in these conditions, the limiting step is the transport rate of product from the reaction site to the aqueous phase. Thus, in the case of CNE the effect is less negative since the reaction rate is lower and the product do not accumulate.

The increase of aqueous phase (which extract the product) flow rate positively influences the biphasic reactor performance. This is because the increase of axial flow rate of extractant phase increases mass transfer of product from the reaction microenvironment (enzymatic-membrane) to the bulk. The removal of the product has the advantages of enhancing the reaction yield and reducing inhibition phenomena.

In addition to the axial flow rate values of the organic and aqueous phases, the flow regime of both phases influences the biphasic membrane reactors performance. In fact, the use of counter-current flow regime improves the reaction rate by increasing mass transfer efficiency. For example, flowing the two phases in counter-current regime along a hollow fiber membrane reactor, an increase of 60% has been obtained with respect to the co-current regime. On the other hand, in co-current flow the two phases are kept stable for longer period of time operation.

The influence of transmembrane pressure (positive from the membrane side containing the substrate) on the efficiency of biphasic membrane reactors has also to be considered. If working at values far below the breakthrough pressure, the effect of transmembrane pressure is not significant. On the other hand, there are ranges of pressure values which affect mass transport and then reaction rate in two separated phase membrane reactors. When working in these ranges, an increase of transmembrane pressure yields to an increase of reaction rate. This is particularly evident when enzyme is immobilized in the sponge layer of asymmetric membranes. Two reasons could explain this behavior: 1) increasing the oil phase pressure, increases the penetration depth in the sponge layer of the membrane and more substrate come in contact with the enzyme; 2) the front reaction is located more inside the sponge layer of the membrane, and the effective diffusion distance for the product to reach the aqueous phase decreases. Using **lipase immobilized** on the surface of

the dense layer, a lower increase of product concentration in the aqueous phase is in general observed with respect to the case when the enzyme is immobilized in the sponge layer. This means that the latter configuration facilitates mass transfer from and to the reaction microenvironment. Furthermore, the higher rate with the enzyme immobilized within the sponge layer, might be related to a better enzyme distribution; the enzyme may be more effective when present as an aqueous solution in the membrane pores compared to when present as gelified on the membrane surface.

References

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