These studies can be divided into two groups, i.e. those involving investigations of the penetration barrier and those related to fatty acids as drug penetration enhancers.

The penetration barrier
A large majority of drugs are absorbed via passive diffusion from the gastrointestinal tract and their bioavailability is closely related to their physicochemical properties. In fact, there are some indications that the efflux and influx pumps, as well as metabolism within the mucosal membrane of the gastrointestinal tract, affects less than 10% of all orally administered drugs. Biological membranes are composed of small amphiphilic molecules, phospholipids with two hydrophobic chains and cholesterol or other related structures, which associate into lipoidal bilayers in aqueous media. The membrane has a relatively hydrophilic exterior and a hydrophobic interior. Drug molecules must possess some lipophilicity to be able to permeate biological membranes, including biological barriers. To facilitate drug permeability through biological membranes it is common to form lipophilic prodrugs of relatively hydrophilic drugs. The hydrophilic membrane exterior is commonly thought to be less important for drug delivery through biological membranes. Current drug penetration enhancers enhance drug delivery through biological membranes (such as skin or mucosa) by causing some physicochemical changes within the lipophilic membrane barrier. However, we have observed that the aqueous exterior of the membranes could be just as effective barrier as the membrane itself. In series of publication we have shown evidence for such aqueous barrier layer. Furthermore we have identified four types of membranes according to the importance of the aqueous diffusion layer for the overall drug diffusion through the membranes.

Some publications


**Drug permeation from aqueous cyclodextrin containing vehicles is frequently both diffusion controlled and membrane controlled.**

Conventional drug penetration enhancers, such as oleic acid, disrupt the structured lipid layers of the biological membrane. Although conventional enhancers are lipophilic they enhance the penetration of both lipophilic and hydrophilic compounds through biological membranes.
Fatty acids form fish liver oil as penetration enhancers

Various marine products, such as fish oils, are rich in unsaturated fatty acids. Approximately 98% of the refined cod-liver oil consists of triglycerides, the rest is unsaponifiable matter, free fatty acids, monoglycerides and diglycerides. The acid part of the glycerides consists mainly of various unsaturated fatty acids, including the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Previously, we have extracted the fatty acids from the cod-liver oil and shown that this extract enhances transdermal and buccal drug delivery. The fatty acid profile of the extract is almost identical to that of the oil. About 17% of the extract consists of saturated fatty acids, mainly palmitic acid (10.4%), and the rest is unsaturated fatty acids such as oleic acid (16.2%), DHA (11.9%), gadonic acid (9.4%), EPA (9.3%), cetoleic acid (7.8%), palmitoleic acid (6.4%) and cis-vaccenic acid (4.4%). We have shown that the penetration enhancing effect of cod-liver oil is associated with the unsaturated fatty acid portion of the extract. Interestingly, cod-liver oil itself does not enhance transdermal drug delivery. Furthermore, the mixture appeared to be better enhancer than the individual acids.

Some publications