34.3.1 Peptide or Protein Conjugation with Hydrophobic Moieties

Various hydrophobic moieties (e.g., simple lipoamino acids [LAA], fatty acids, etc.) have been applied to improve skin delivery of peptides and proteins. Simple LAA is a single amino acid that is combined with a fatty acid (Xia 2001), but fatty acids are straight hydrocarbon chains with a functional group of carboxylic acid. Butyric acid (C4), caproic acid (C6), octanoic acid (C8), lauric acid (C12), myristic acid (C14), palmitic acid (C16), stearic acid (C18), oleic acid (C18), C6 LAA, C8 LAA, and C10 LAA are some hydrophobic moieties that have been used to increase skin permeation of peptides and proteins (see Table 34.1) (Caccetta et al. 2006; Choi et al. 2014; Foldvari et al. 1998, 1999; Gozes et al. 1994; Namjoshi et al. 2014; Setoh et al. 1995; Toth et al. 1995; Yamamoto et al. 2003). The chemical structures of some parent peptides that have undergone chemical modification are presented in Figure 34.1.

LAAs, which possess the structural characteristics of lipids and α-amino acids, can increase percutaneous drug absorption (Ziora et al. 2012). Namjoshi et al. (2014) applied a racemic mixture of LAAs (carbon chain length C6, C8, and C10) for conjugation to the tetrapeptide AAPV (Ala-Ala-Pro-Val), a human neutrophil elastase inhibitor. Human epidermal permeation of all conjugates exceeded that of AAPV. The ability for epidermal permeation of AAPV and its derivatives was in the following order: C8 (D,L)-LAA-AAPV > C10 (D,L)-LAA-AAPV > C6 (D,L)-LAA-AAPV > AAPV. The authors concluded that there is an optimal carbon chain length for skin permeation. The stereoselective epidermal permeation was also reported so that the D-diastereomers were

TABLE 34.1
Examples of Chemically Modified Peptides and Proteins by Hydrophobic Moieties

Peptide or Protein Name	MW (Da)	Length (aa)	Conjugated Moiety (Carbon Atoms Number)	Permeation Study Type	Formulation Vehicle	Reference
Phe-Gly	222.2	2	Short-chain fatty acids (C4,C6,C8)	Franz-diffusion cells (statistic)	Not mentioned	(Yamamoto et al. 2003)
AAPV	356.4	4	Short-chain LAAs (C6, C8, and C10) and short-chain fatty acids (C7)	Franz-diffusion cells (statistic)	Propylene glycol	(Caccetta et al. 2006; Namjoshi et al. 2014; Rocco et al. 2016)
TRH	362.4	3	Chloroformate (C5, C9)	Franz-diffusion cells (statistic)	Phosphate buffer or propylene glycol	(Møss & Bundgaard 1990)
KTTKS	563.6	5	Long-chain fatty acid (C16)	Franz-diffusion cells (statistic)	15% ethanol	(Choi et al. 2014)
Tetragastrin	596.7	4	Short-chain fatty acids (C2,C4,C6)	Franz-diffusion cells (statistic)	Not mentioned	(Setoh et al. 1995)
[D-Lys]^6 GnRH	1253.4	10	Short- and long-chain fatty acids (C2, C6, C12, C18)	Measurement of LH level in the blood	DMSO	(Yahalom et al. 1999)
VIP	3326.8	28	Long-chain fatty acid (C18)	Distribution measurement of radioactively labeled compounds in the various organs	I-Monocapryloyl-rac-glycerol and DMSO	(Gozes et al. 1994)
IFN-α2b	19271	165	Long-chain fatty acid (C16)	Franz-diffusion cells (flow-through)	Phosphate buffer or methylcellulose gel hydrated with phosphate buffer	(Foldvari et al. 1998)