and high molecular weight (Benson & Namjoshi 2008; Gorouhi & Maibach 2009; Zhou et al. 2017). To overcome these problems, various approaches have been applied from penetration enhancers to physical methods (Amsden & Goosen 1995; Benson & Namjoshi 2008; Kalluri & Banga 2011).

Here, the possibility of skin permeation of peptides and proteins and chemical modification approaches for the enhancement of transdermal and topical delivery of these difficult molecules are reviewed.

## 34.2 SKIN PERMEATION OF PEPTIDES AND PROTEINS

Given the nature of the intercellular space, hydrophobic compounds are more appropriate to permeate across the intact stratum corneum than hydrophilic compounds, but considering the permeation process, a balance between hydrophilicity and hydrophobicity is essential to cross the skin (Subedi et al. 2010). Hence, there is an optimum value for hydrophobicity so that the desired log partition coefficient (1-octanol/water) is in the range of 1 to 3. In addition to hydrophobicity, another important limitation is to have a molecular weight of approximately less than 500 Da (Gujjar et al. 2016; Subedi et al. 2010). As a result, peptides and proteins are not good candidates for topical/transdermal delivery due to their high molecular size and hydrophilic nature (Falconer & Toth 2007). Apart from these, the peptides and proteins are mainly charged molecules at physiological pH (Benson & Namjoshi 2008) and in this respect also they are not suitable for crossing the skin (Wang et al. 2005).

Different approaches have been applied to increase skin permeation of peptides and proteins. These approaches include application of chemical penetration enhancers, encapsulation into hydrophobic carriers, physical enhancement methods, and chemical modification. The first three strategies have been extensively reviewed (Alexander et al. 2012; Naik et al. 2000; Singh et al. 2012), but there is a considerable absence of information about research performed in the field of chemical modification of peptides and proteins. However, chemical modification could increase the metabolic and chemical stability (Bundgaard & Møss 1999; Toth et al. 1994), as well as skin absorption of peptides and proteins (Foldvari et al. 1998; Møss & Bundgaard 1990). Thus, the investigations on the influences of chemical modification on biological activity, enzymatic stability, and skin permeation are comprehensively reviewed here.

## 34.3 CHEMICAL MODIFICATION OF PEPTIDES AND PROTEINS

Chemical modification can be defined as a process in which a chemical moiety is incorporated into the native structure of peptides or proteins (Buckley et al. 2016). Such modifications can be used to increase the permeability of molecules across biological barriers, as well as to increase the metabolic or enzymatic stability. The two main categories of chemical moieties that have been employed to date for the improvement of topical and transdermal delivery of peptides and proteins include hydrophobic moieties and cell-penetrating peptides (CPPs). Thus, two approaches are discussed here.

From a mechanistic view, hydrophobic moieties increase the tendency of peptides and proteins to the intercellular lipid matrix by enhancing the partition coefficient of these macromolecules. In fact, they change the physicochemical properties of peptides and proteins. CPPs act in a different manner; they decrease the resistance of the diffusional barrier (intercellular lipid matrix and keratins) and consequently increase the diffusion coefficient of peptides and proteins.