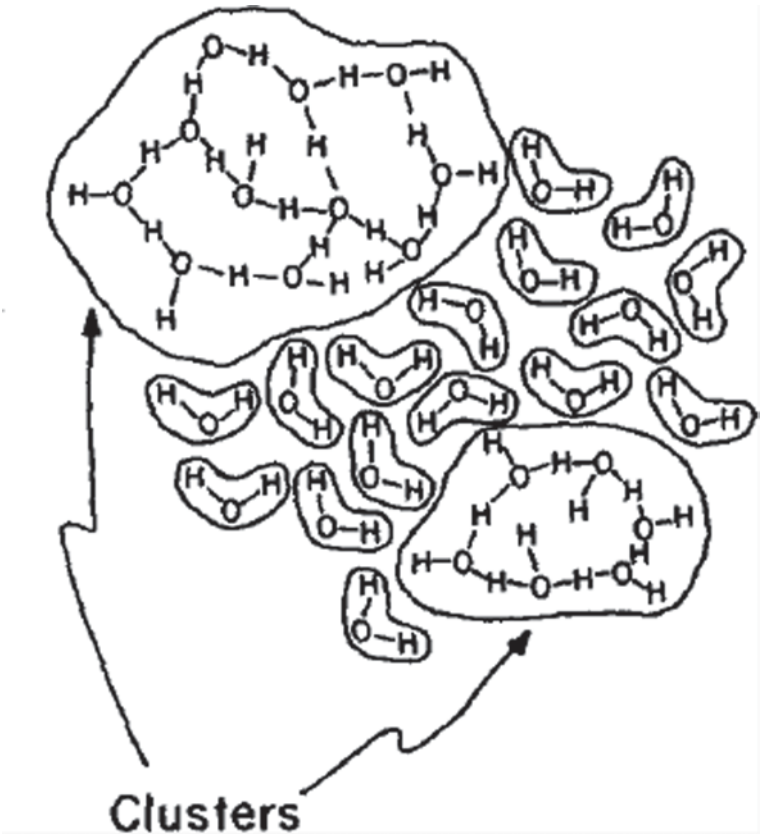

Fig. 2 Schematic representation of the model of liquid water, showing hydrogen-bonded clusters and unclustered water molecules. The molecules in the interior of the clusters are tetracoordinated, but not drawn as such in this two-dimensional diagram. The representation is based on the Frank–Wen model of liquid water (Reproduced with permission from [54]. Copyright 2014, AIP Publishing LLC)

values of β_{kww} from 0.3 to 0.8, indicating a broad distribution of relaxation times and significant inhomogeneity.

Domains with different relaxation times may also have different degradation rates. Note that heterogeneity in freeze-dried amorphous materials can be easily observed by DSC. Indeed, DSC traces of such samples are commonly reveal sub-T_g transition, which can be eliminated by thermal cycling (i.e., heating above the T_g followed by quenching) or annealing below the T_g [56]. In this respect, it is possible that the high-temperature annealing, which was shown to improve stability of both proteins and small molecules, [57–62] reduces population of the least stable molecules thus resulting in the decrease of an average degradation rate.

An experimental observation of large-scale heterogeneities developed after cooling a model system (concentrated sorbitol/water solution) below its T_g was reported