

Definition, Functional Role, and Classification

Buffers are commonly used in freeze-dried dosage forms to control pH, in order to improve the long-term stability of protein. Knowing pH of maximum stability is a critical requirement for achieving a stable formulation. During the formulation development, buffering capacity and the potential for buffer catalysis are two main buffer properties to consider. The general rule of thumb is not to exceed the effective buffer capacity by maintaining pH within one unit from its pK_a [39]. For freeze-dried products, special consideration needs to be made for buffer selection including buffer crystallization during freezing, impact on collapse temperature of the freeze-concentrated solution and T_g (glass transition temperature) of the dried formulation, and the volatility of the buffer components under vacuum [40].

Most lyophilized products on the market are formulated in the pH range from 4 to 8 [18]. Common buffers and their pH range are listed in Table 2.

During the selection of buffer system for freeze-dried formulations, it is essential to minimize changes in the pH and apparent pH during freezing and drying. Changes in apparent acidity can lead to acceleration of drug degradation, either directly, via specific acid/base catalysis, or indirectly, by changing ionization state of the protein and thus making it potentially more susceptible to both physical (e.g., aggregation) and chemical (e.g., oxidation) degradation pathways. The propensity for crystallization of buffer components during freezing is the most commonly recognized root cause for pH shifts. It is widely known, for example, that in frozen phosphate buffer solutions, crystallization of disodium hydrogen dodecahydrate ($Na_2HPO_4 \cdot 12 H_2O$) causes a pronounced acidic pH shift in the freeze-concentrate [20, 37, 48]. Similarly, the pH swing, with pH jumping from 4 to 8 followed by major drop to pH 2, was observed in frozen succinate buffer solutions and attributed to sequential crystallization of the buffer components [47].

Table 2 Common buffers and their pH buffering range

Buffer	Type	Approximate buffering range
Sodium phosphate	Phosphate	6.2–8.2 [15]
Sodium acetate	Carboxylic acid salt	3.8–5.8 [15]
Sodium citrate	Carboxylic acid salt	2.1–6.2 [15]
Glycolate	Carboxylic acid	2.6–4.6 [15]
Malate	Carboxylic acid	2.4–6.1 [15]
Succinate	Carboxylic acid	3.2–6.6 [15]
Glutamic acid	Amino acid	2–5.3 [15]
L-histidine	Amino acid	5.0–7.0 [25]
Glycine	Amino acid	8.8–10.8 [15]
Tris	Amine	7.1–9.1 [15]
TEA (triethanolamine)	Amine	7–9 [15]
Citrate-phosphate	Combination	2.2–8.0