Table 16: Surfactants: Control, Use, and Characterization

Facilitators –

Patricia Lewis, Omeros Corporation

Linda Yi, Biogen

Scope:

Polysorbates (PS), especially polysorbate 20 (PS20) and polysorbate 80 (PS80), are the most widely used surfactants in biopharmaceutical formulation. Commercially available PS are chemically diverse mixtures. Relative abundance of PS subspecies tends to vary from different vendors due to differences in raw material and PS manufacturing process being used. Polysorbates may degrade through (auto-) oxidation, chemically, or enzymatically induced hydrolysis. This in turn may inadvertently affect quality, stability, efficacy, and safety of the proteins. Therefore, it is crucial to develop sound PS control strategies to minimize PS degradation and assure adequate PS content in formulated product throughout its intended shelf life.

This roundtable aims to discuss PS control strategy that has been or is to be deployed with respect to PS usage and characterization, the challenges associated with the control strategy implementation.

Questions for Discussion:

1. Degradation:
    a. What are the potential consequences of PS degradation and how have you mitigated the risks?
    b. How to determine if the degradation is induced by oxidation, or hydrolysis (chemical or enzymatic)?
    c. What are the analytical tools available to determine degradation mechanisms?
    d. Which methods would you include in your stability/release testing for routine monitoring and quantity?
    e. What are the challenges in method qualification/validation and critical reagent management?
    f. How do you demonstrate stability indicating properties for any method?
    g. What are the strategies to define specifications (release, stability?)
    h. Any strategies to navigate regulatory filings when degradation is observed but still within specifications?

2. Control Strategy Approaches:
    a. What elements should be included in a PS control strategy? Any challenges associated with its implementation?
3. Any preferences polysorbate raw material available, e.g. Multi-Compendium grade, Chinese Pharmacopeia grade, super refine grade.
    a. Any preferences grade? why?
    b. PS raw material controls?

Discussion Notes:

January 25 and 27, February 2 and 4 *combined*–

Attendees: representatives from FDA, consultant, and multiple industrial labs

QUESTIONS:

1. Degradation:

a. What are the potential consequences of PS degradation and how have you mitigated the risks?

PS hydrolysis leads to release of free fatty acid that may form subvisible or visible particle, which may adversely affect product quality, stability etc. PS oxidation may not affect its function as protein stabilizer (excluding the peroxide-induced oxidation etc), but it may affect how PS content method performs.

Mitigation strategy would involve process development (cell culture, cell line, purification, formulation) and analytical controls, but identification of root cause is the key for mitigation strategy. PS alternatives has been explored by a number of companies.

Q: PS degradation via hydrolysis pathway became more prominent in the past few years, why?

A: not sure, high protein concentration formulation? The pursuit of high titer process? Media change to chemically defined media?

b. How to determine if the degradation is induced by oxidation, or hydrolysis (chemical or enzymatic)?

Typical PS content method has certain capability of detecting degradation, but not at the beginning of the degradation. Whereas PS profiling method would be a better way to identify the degradation pathway.

Q: In the case of hydrolysis pathway, is it needed to perform free fatty acid method to orthogonal confirm?

A: Yes, if the method is available, but not all companies have the free fatty acid method readily available. The hydrolysis degradation pathway can be inferred based on the profile change, LC-MS based PS profiling method is able to positively confirm the degradation pathway.

c. What are the analytical tools available to determine degradation mechanisms?

PS profiling method is able to resolve PS subspecies into several peaks, the profile change can be used to identify degradation pathway. However, sometimes, the profiling method may have carry over issue, and water blank injection is required in between to minimize carry over issue.

d. Which methods would you include in your stability/release testing for routine monitoring and quantity?

PS content method used for release and/or stability especially for late or commercial programs. Whereas, PS content method may be used as characterization method for early phase programs;

Q: Do you use PS profiling method in support stability study?

A: maybe not, only if PS content decrease was observed.

e. What are the challenges in method qualification/validation and critical reagent management?

For some PS content method, QL might be too high to be useful in some cases. For some PS content method, it requires PS raw material from the same vendor and/or same lot as calibrant, making it challenge to manage the testing and sourcing of the critical reagent.

Lacking of proper PS reference standard was brought up during the discussion. Will there be any interest to form a task force to come up a PS reference standard from USP? The PS reference standard can serve as calibrant, and may solve some of the method issue noted above.

USP published a polysorbate stimuli article “understanding the composition and quality of polysorbates to strength USP-NF compendial standard” on 05Jan2021, which is now open for commenting.

f. How do you demonstrate stability indicating properties for any method?

Typical forced degradation study may be applied such as acid, base, temp, light, oxidant etc to see how PS method performs.

g. What are the strategies to define specifications (release, stability?)

Formulation DOE study is beneficial to define the lower limit of PS. Shipping studies performed at lower PS80 level is helpful to support justification. For early phase program, platform knowledge/experience may apply.

h. Any strategies to navigate regulatory filings when degradation is observed but still within specifications?

It is still important to identify the root cause; also need to make sure other product quality, stability were not affected. Need to understand the degradant, and their impact product quality, efficacy; what are those degradants affect on other method you are performing; it would be easier to navigate regulatory filling with those info, e.g. “the known”.

2. Control Strategy Approaches:

a. What elements should be included in a PS control strategy? Any challenges associated with its implementation?

PS control strategy may contain Raw material, manufacturing process control, analytical toolbox etc.

Some challenge may be associated with logistics. For example, PS raw material may be prone to auto-oxidation, and therefore needs to be stored under N2 overlay, protected from light etc after opening the bottle. Some companies may adopt single use PS raw material bottle to save the cost of setting up proper N2 overlay etc in manufacturing.

3. Any preferences polysorbate raw material available, e.g. Multi-Compendium grade, Chinese Pharmacopeia grade, super refine grade.

a. Any preferences grade? why?

MC PS works just fine, but high purity PS was required to register biologic drugs in China since 2015. It was found that high purity PS20 may be less prone to oxidation degradation.

With the update of ChP monograph on PS in 2020, high purity PS is no longer needed. However, it sets ethylene glycol and dietheylene glycol limit as no greater than 0.01%, and USP and EP has no limit test on both.

b. PS raw material controls?

Single use PS raw material bottle is preferred for a number of companies.