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An Approach to Control Strategies for Sulfonate Ester Formation in Pharmaceutical Manufacturing Based on Recent Scientific Understanding

David Elder,[†] Kevin L. Facchine,[‡] Jeffrey N. Levy,[§] Rodney Parsons,[⊥] David Ridge,[∥] Lesley Semo,[§] and Andrew Teasdale*[,□,¶]

[†]GlaxoSmithKline - UK, Park Road, Ware, Hertfordshire, SG12 0DP, United Kingdom

[‡]GlaxoSmithKline - U.S.A., Five Moore Drive, Research Triangle Park, North Carolina 27709-3398, United States

[§]Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285, United States

[⊥]Bristol-Myers Squibb Co., One Squibb Drive, New Brunswick, New Jersey 08903, United States

[∥]Hoffmann-La-Roche, Inc., 340 Kingsland Street, Nutley, New Jersey 07110, United States

[¶]AstraZeneca, Charter Way, Silk Road Business Park, Macclesfield, Cheshire, SK10 2NX, United Kingdom

ABSTRACT: The issue of sulfonate ester formation is one that has been of significant concern to regulatory authorities since the start of the millennia. These concerns, focused primarily on the risk of ester formation where sulfonic acid salts are formed in alcoholic solvents, has led to the need for specific analysis for such species in the final API in any product containing a sulfonic acid counterion. This concept article examines the growing experimental data that exist showing how this risk can be negated through the application of simple process controls that effectively eliminate this risk. These data are also compared to specific product data, illustrating the practical experience of organizations. The article also reflects on the Viracept incident and how the mechanistic understanding of the reaction between sulfonic acids and alcohols readily predicts the observed outcome. It is the conclusion of the authors that the continued need for exhaustive analytical testing should be replaced instead by a scientific risk-based approach, taking into full consideration the specific process conditions.

■ INTRODUCTION

Since the turn of the new millennium, regulatory authorities and pharmaceutical companies have become increasingly concerned over the possible presence of genotoxic impurities in pharmaceuticals. Within the arena of genotoxic impurities, one class which has received a great deal of scrutiny is sulfonate esters, impurities potentially formed by the reaction between a sulfonic acid and an alcohol. The widespread use of such acids as salt counterions and the presence or use of alcoholic solvents in the associated salt formation process has intensified this concern. Such concerns appeared to be vindicated when Roche reported the ethyl methane sulfonate (EMS) contamination of Viracept,[1,2] leading to even greater scrutiny.

This concept article will evaluate the level of actual risk of patient exposure to sulfonate esters through examination of the studies performed by a Working Group within the Product Quality Research Institute (PQRI). These studies have examined in detail the reaction mechanism and processing parameters that govern the formation of sulfonate esters.[3,4] This article will review the key findings from these studies and link these findings to general quality by design (QbD) principles that may be used to determine appropriate control strategies to prevent sulfonate ester formation. In the final part of the report we reflect on the Viracept incident and examine how the results of the PQRI studies correlate fully with the observed EMS contamination.

■ THE IMPORTANCE OF SULFONATE SALTS

A significant portion of drugs that are currently marketed or are in development are either weak organic bases or acids; these can therefore exist as a number of different pharmaceutically acceptable salts. Salt formation is an extremely useful approach for the optimization and/or modification of the physicochemical, biopharmaceutical, therapeutic, and processing properties of these ionisable drug substances. The list of potential active pharmaceutical ingredient (API) properties that generally depend on counterion selection includes the following: crystallinity, chemical purity, solubility, stability, manufacturability, and drug product performance. Sulfonic acid salts often exhibit more desirable chemical or physical properties than other salts of the same organic base. Given the myriad of considerations and the superior performance demonstrated in a number of examples, it is clear that sulfonic acids have an important role in pharmaceutically useful salt formation.[5]

Serajuddin[6] reported a general increase in the usage of strong inorganic counterions, for example mesylates, hydrochlorides, hydrobromides, etc., which now account for just over three-quarters of the total usage of salts. He ascribed this increased usage to the general decrease in aqueous solubility of new drug candidates. The intrinsic solubility (S_0) of the API is in turn linked with the pH of maximum solubility (pH_{max}) and decreases in S_0 lead to commensurate decreases in pH_{max} of the

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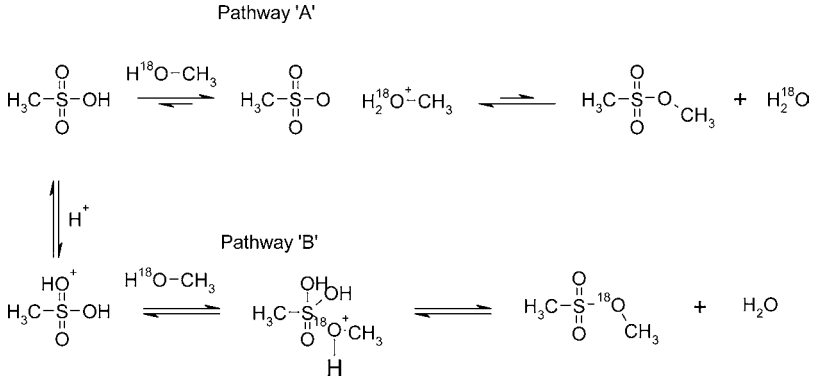

Figure 1. Potential reaction pathways associated with the formation of the sulfonate ester MMS.

resultant salts. If the pH_{max} falls below the pK_a of standard carboxylic acids (~pH 4.5−5), then salt formation with these counterions will be affected and only strong inorganic acids will have low enough pK_a's to permit salt formation to occur. Removing the potential to use sulfonic acids on the basis of theoretical safety concerns would severely restrict the scope of such candidates.

FORMATION OF SULFONATE ESTER

Prior to the studies performed by the PQRI group, there was no clear understanding of the mechanism involved in sulfonate ester formation. To elucidate the mechanism, a series of elegant experiments were carried out using isotopically labelled (^{18}O) methanol and methanesulfonic acid. Two possible reaction pathways were considered, illustrated below in Figure 1.

Mass spectral analysis of the reaction showed that the ^{18}O label was not present in the methyl methanesulfonate (MMS) formed: the ^{18}O was only detected in the water. This supports the conclusion that the reaction mechanism for the formation of sulfonate esters followed pathway 'A'. The critical conclusion from these studies is that a key step in the formation of methyl mesylate involves the protonation of methanol;[7] this is directly influenced by acidity. In other words, sulfonate esters can only be formed under extreme reaction conditions which lead to protonation of the alcoholic solvent. Subsequent studies detailed in the appendix confirmed this conclusion and also demonstrate that this mechanistic model enables the use of simple process controls to avoid sulfonate ester formation and thus effectively eliminate the risk of formation for these genotoxic impurities.

Sulfonate ester formation as illustrated above is mediated by a number of factors; these include temperature, water content, and most significantly, acidity. A detailed investigation into these factors has been performed on a series of alkyl and aryl sulfonate esters by the PQRI working group. The output from these studies has been used to illustrate the effect these parameters have on levels of ester formed across a range of sulfonic acid/alcohol systems.[3,4] Those relating to methyl methanesulfonate are exemplified below.

Not surprisingly, lowering the temperature (for example, operating at 40 °C instead of 60 °C) significantly reduces the rate of formation and thus the level of ester produced. On the basis of the activation energies determined for a series of methanesulfonate esters, this is found to be on the order of a 4-fold reduction for a 10 °C reduction in temperature under the most favorable conditions (anhydrous, no base, and neglecting solvolysis). Minimizing the residence time of the sulfonic acid in alcoholic solution can dramatically reduce the level of ester formed as well. With regards to water, the presence of even moderate levels of about 7% w/w reduced the levels of MMS by an approximate 3-fold factor, forming less than 1000 ppm MMS on a molar basis at 60 °C after 30 h.[4]

Sulfonate ester formation is observed under strongly acidic conditions, but at levels below 1% in solution under anhydrous conditions and in typical ranges of time and temperature (overnight at up to 70 °C). As discussed above, reductions in time and temperature and the addition of even small amounts of water can reduce formation rates and solution levels many fold. Similarly, conditions of relatively low acidity found in normal, well-controlled, acid−base-induced crystallization processes also significantly reduce sulfonate ester formation. This is the most important factor when considering how to effectively minimize or eliminate the formation of sulfonate esters in sulfonate salt-forming reactions. Salt formations using sulfonic acid counterions often employ either stoichiometric amounts or small excesses of acid. The formation of MMS under conditions of lower acidity was tested using the weak base 2,6-lutidine as a surrogate for a pharmaceutically active weak base. (As an extremely weak base, 2,6-lutidine is less likely to suppress formation of sulfonate esters than most pharmaceutically useful bases and represents perhaps a worst case in terms of evaluating solution acidity.) Partial neutralization of methanesulfonic acid with about 0.8 mol equiv of 2,6-lutidine significantly reduced the extent of ester formation, consistent with the established mechanistic model for this acid-catalyzed reaction. This composition corresponds to methanesulfonate salt formation using approximately 20 mol % excesses of acid. In the 20-h period studied, the molar conversion to the sulfonate ester amounted to ~0.06% at the highest temperature (compared with levels of 0.26% in the absence of base at a similar time-point—nearly a 5-fold reduction). Additional experiments were performed using a slight (~0.08) molar excess of base at temperatures of 40 °C, 50 °C, 60 °C, and 70 °C over 20 h. In all of the samples, no detectable level of MMS was observed (<20 ppm in solution on a molar basis). The formation of sulfonate ester is totally suppressed through base sequestration of the acidic catalyst. Where an excess of base is employed, this effectively eliminates formation of sulfonate esters.[4]

The studies of other sulfonic acid/alcohol systems[4] exactly mirror the findings of the initial MMS studies.[3] In evaluating the results of these studies, it is important to point out that the sulfonate ester levels were determined in solution and do not take into account the significant reduction expected in the

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Table 1. Sulfonate ester formation in the manufacture of several active pharmaceutical ingredients

manufacturing step	class of amine	sulfonic acid[a]	stoichiometry (equiv of acid)	solvent (vol)	temp. (°C)	water added	daily exposure limit (μg)[b]
final	secondary	CSA	0.95	ethyl acetate	45−55	none	<0.1 (AZ)[c]
final	secondary	MSA	0.95	isopropyl alcohol/ethanol	up to 60 cooled to 20	none	<1.5 (AZ)[c]
final	tertiary	MSA	1.1	butanol, MSA added as aq soln (70% w/w)	up to 90	∼5% w/w	<1.5 (AZ)[c]
final	primary	MSA	1.05	methanol, butyl acetate	methanol reflux	7.5 mol equiv (to aid crystallization)	0.20 MMS 0. 22 EMS (AZ)
final	primary	BSA	1.0	isopropyl acetate/ipa	40	none	<0.1 (AZ)[c]
penultimate	tertiary	MSA	1.2	isopropyl alcohol (8)	60	none	<0.08 (BMS)[c]
final	tertiary	MSA	0.9−1.2	methanol (10−15), ipa	45−55	none	<0.02 (Lilly)[c]
penultimate	primary	pTSA	1.0	isopropyl alcohol (10)	70	trace from pTSA	<1.5 (GSK)[c]
final	tertiary	MSA	1.0	ethanol (20−30)	up to 82	none	<1.5 (Roche)[c]
final	tertiary	MSA	0.970−0.995	ethanol (∼25)	6−35	none	<1.5 (Roche)[c]

[a]BSA = benzenesulfonic acid; CSA = camphorsulphonic acid; MSA = methanesulfonic acid; pTSA = *p*-toluenesulfonic acid. [b]Data from AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Pfizer, and Roche. [c]Values reflect the detection limit of the method employed.

isolation/filtering of the solid API salt from the crystallization solution and subsequent washes to remove residual mother liquors.

CONTROL OF SULFONATE ESTER FORMATION

The results of the PQRI studies[3,4] led to the following control strategy for minimizing sulfonate ester formation to the lowest practical level during the formation of an API sulfonate salt in the presence of an alcohol:

(1) Avoid an excess of acid to minimize the potential for sulfonate ester formation.
(2) If an excess of sulfonic acid is needed, use the minimum excess possible, conduct the salt formation and isolation steps at the lowest practical temperature, and restrict the reaction time to as low as reasonably practicable.
(3) If possible, include water in the salt formation and isolation procedures to shift the esterification equilibrium towards acid and alcohol.
(4) Add the sulfonic acid slowly to the dissolved base, ensuring that mixing conditions are optimal.[8]
(5) Avoid situations in which sulfonic acid and alcohol are mixed and stored before use.

Use of the mechanistic model in collaboration with control of the critical process parameters that impact the rate of formation of sulfonate esters forms the foundation of a control strategy that minimizes or potentially eliminates the need for analytical testing. With limited process understanding, analytical testing of the API is often required to demonstrate absence of genotoxic impurities. Leveraging the PQRI work and QbD principles to establish the proper design space should render analytical testing of the API an unnecessary part of the overall control strategy. This QbD approach can be extended to any process and should form the primary means to ensure control of impurities wherever possible.

DATA ON PRODUCTS

In the absence of this recently developed mechanistic understanding, the pharmaceutical industry has tested a number of products which are synthesized under conditions which might have been expected to cause formation of sulfonate esters. Table 1 shows sulfonate ester data of APIs from the authors' companies. Consistent with the mechanistic understanding, sulfonate esters are not detected when salts are formed under appropriate, controlled conditions. It is important to stress that these data relate to processes which were developed prior to the current understanding of sulfonate ester formation: future processes can be optimized with this knowledge in mind. Despite this, there is still clear evidence that, even where no conscious process control was applied, levels of sulfonate esters were not a concern. Incorporation of the mechanistic understanding of sulfonate ester formation into design spaces for new products will reduce the theoretical risk even further.

VIRACEPT

The 2006 temporary withdrawal of Viracept (a methane sulfonate salt) as a result of significant contamination with ethyl methane sulfonate (EMS) heightened concern for sulfonate ester formation.[1,2] Close examination of the Viracept incident shows that the conditions under which EMS formed were significantly different to those encountered under controlled salt formation conditions. In the case of Viracept, EMS formed as a result of prolonged contact between a small amount of residual ethanol (present as a result of a cleaning process) and a tremendous excess of methane sulfonic acid (MSA) in a tank used to store MSA. Under normal processing conditions the reverse is in effect true. Rather than a vast excess of acid (and hence of protons to catalyze the esterification reaction), the level of acidity is restricted, especially where a base (the API) is present in the system. In addition, during a typical crystallization, there are very large volumes of the alcoholic solvent, relative to a very small amount of acid.

The key role that water plays in the decomposition of the alkyl sulfonate ester (hydrolysis to corresponding sulfonic acid and alcohol) has also been investigated.[8] The EMS decomposition rate in Viracept™ tablets was reported as being 0.3%/day (approximately 9% month) at 25 °C and 0.2%/day (approximately 5%/month at 20 °C.

Therefore, rather than contradicting the PQRI studies, given the clear mechanistic evidence that ester formation is acid mediated, the studies would in fact predict the possible formation of relatively high levels of sulfonate esters under the highly acidic, abnormal conditions present in the process leading to the Viracept contamination.

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CONCLUSION

Through the elucidation of the reaction mechanism for sulfonate ester formation it has been possible to determine the key factors that affect the reaction and to demonstrate that with consideration of the critical process design parameters (e.g., stoichiometry/acidity/temperature/water content and reaction time), alkyl sulfonate ester formation can be controlled to such an extent as to render the risk of their formation inconsequential. This purposeful use of the mechanistic model and process design in concert provide the foundation to the control strategy that minimizes/avoids potential formation of sulfonate esters. Experimental data on products confirms the absence of sulfonate esters in products made under appropriate, controlled conditions. The knowledge of how to control these parameters can be used when creating the design space of future molecules. By designing reaction conditions with the appropriate acidity, stoichiometry, temperature, and water content, one will be assured that ester formation will not be an issue. By using reaction conditions that effectively inhibit ester formation, the need to test for sulfonate esters may no longer be necessary during product development and commercial manufacturing.

AUTHOR INFORMATION

Corresponding Author

*andrew.teasdale@astrazeneca.com

Notes

The authors declare no competing financial interest.

□Leader of PQRI Sulfonate Ester Evaluation Working Group

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