Scientific Research Publishing

American Journal of Analytical Chemistry, 2020, 11, 363-375
https://www.scirp.org/journal/ajac
ISSN Online: 2156-8278
ISSN Print: 2156-8251

Forced Degradation Studies on Sodium Picosulfate and Separation of 15 Process Related Impurities/Degradants by HPLC

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How to cite this paper: Patel, P., Hotha, K.K., Patel, D., Kamma, J., Gudimella, A., Bompelliwar, S. and Ramamoorthy, S. (2020) Forced Degradation Studies on Sodium Picosulfate and Separation of 15 Process Related Impurities/Degradants by HPLC. *American Journal of Analytical Chemistry*, **11**, 363-375.
https://doi.org/10.4236/ajac.2020.1111029

Received: October 30, 2020
Accepted: November 24, 2020
Published: November 27, 2020

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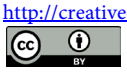

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Abstract

A selective, precise and stability-indicating, high performance liquid chromatographic method was developed for the analysis of active ingredient sodium Picosulfate and forced degradation behavior was studied. The current article describes forced degradation behavior of the Sodium Picosulfate drug substance in detail by analyzing 15 process related/degradants in a single HPLC method under ICH recommended stressed conditions. Mobile phase comprised of 0.01 M of Disodium hydrogen phosphate and 0.01 M of potassium phosphate monobasic buffer and 1 mL of triethyl amine in 1000 mL water adjusted to pH 7.5 with 10% phosphoric acid. Acetonitrile was used as Mobile Phase B. The separation was achieved on a gradient method. The reversed phase chromatography was performed in Hypersil BDS C18 5.0 µm, 4.6 × 250 mm column maintained at temperature 35˚C. Injection volume was 60 µL. Milli-Q water used as diluent. The mobile phase was pumped at 0.9 mL/min^{-1}. The eluted compounds were monitored at 220 nm. Secondary wavelength of the 263 nm was studied to check any further degradants during the forced degradation studies. New additional degradants Sodium Picosulfate Benzyl alcohol Impurity and N oxide degradations were discussed and studied during the forced degradation to understand the chemical stability of the drug substance.

Keywords

Sodium Picosulfate, Chemical Degradation, Forced Degradation, Benzyl Alcohol Impurity

1. Introduction

Sodium Picosulfate 4,4'-(2-pyridylmethylene) diphenyl bis (hydrogen sulfate)

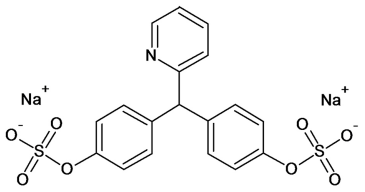
disodium [Figure 1] belongs to a drug class known as a stimulant laxative [1] [2]. After being taken orally, it is metabolized into 4,4'-dihydroxydiphenyl-(2-pyridiyl) methane by the bacteria naturally present in the large intestine. It then stimulates nerve endings in the intestinal wall. These nerves make the muscles in the intestine and rectum contract more often and with more force, a process known as peristalsis. This moves the contents of the intestine along so that the bowel can be emptied, and hence relieves constipation. Sodium Picosulfate is also used to stimulate the emptying of the bowel before surgery [3].

There were several analytical methods available in the literature for the quantification of Sodium Picosulfate. Methods of analysis for Sodium Picosulfate which have been described in the literature are mostly based on TLC [4] [5] [6], GC/MS [7], HPLC with diode array detection [8] [9], Capillary electrophoresis techniques [10] and LC-MS [11]. Thermal oxidation, alkaline degradations of the Sodium Picosulfate were studied by HPLC to identify the degradation of the drug substance [12] [13]. However, the article doesn't clearly describe the process related impurities and further degradants that can arise during the stability. The current article describes forced degradation behavior of the Sodium Picosulfate drug substance in detail by analyzing 15 process related/degradants in a single HPLC method [Figure 2(a) & Figure 2(b)]. The methodology has been developed considering all the synthetic impurities that could arise during the manufacturing of the drug substance and possible degradants which could during the stability storage of the drug substance. Forced degradation study was performed and the formation of the impurities under different degradation conditions is discussed in detail. New additional degradants Sodium Picosulfate Benzyl alcohol Impurity and N oxide degradations were discussed and separated by HPLC method along with the other Process related Impurities/degradants. Additional N oxide impurities were studied during the forced degradation to understand the chemical stability of the drug substance. This is the first article of its kind for the sodium Picosulfate drug substance that can provide the chemical stability of the drug substance as well as precise analytical method that can separate 15 impurities.

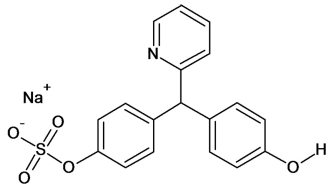
2. Experimental

Chemical and Reagents

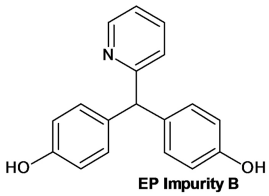
Sodium Picosulfate standard was supplied by USP and impurity standards were supplied by TLC Pharmaceutical Company, Ontario, Canada. Potassium Dihydrogen phosphate and Disodium Hydrogen phosphate were purchased from Sigma Aldrich and Spectrum respectively. The HPLC grade acetonitrile, methanol, were purchased from J.T Baker and Spectrum respectively. Water used was obtained by using Millipore MilliQ Plus water purification system. Equipment HPLC coupled with PDA detector and equipped with empower software (Waters Corporation, Milford, USA) was used for the identification of unknown compounds formed during forced degradation and stability testing studies.



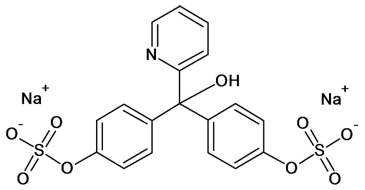
Sodium Picosulfate
Molecular Formula: $C_{18}H_{13}NO_8S_2$
Formula Weight: 435.42



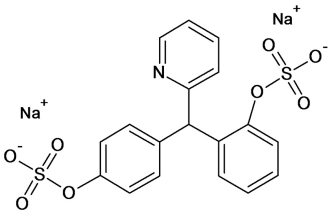
EP Impurity-A
Molecular Formula: $C_{18}H_{14}NNaO_5S$
Formula Weight: 379.36



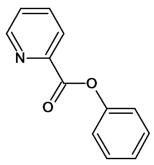
EP Impurity B
Molecular Formula: $C_{18}H_{15}NO_2$
Formula Weight: 277.31



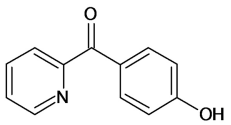
SPS Benzyl alcohol
Molecular Formula: $C_{18}H_{13}NNa_2O_9S_2$
Formula Weight: 497.40



EP Impurity C Disodium salt
Molecular Formula: $C_{18}H_{13}NNa_2O_8S_2$
Formula Weight: 481.40



Picosulfate Impurity-2
Molecular Formula: $C_{12}H_9NO_2$
Formula Weight: 199.20



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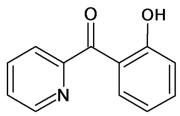

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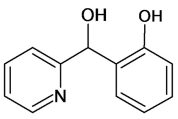
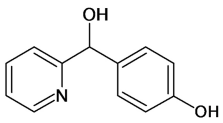
Formula Weight: 199.20



Picosulfate Impurity-5
Molecular Formula: $C_{12}H_{11}NO_2$
Formula Weight: 201.22



Picosulfate Impurity-6
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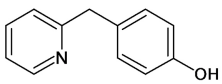
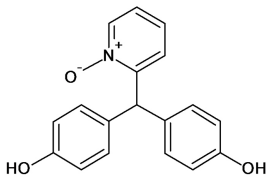
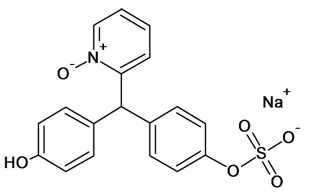


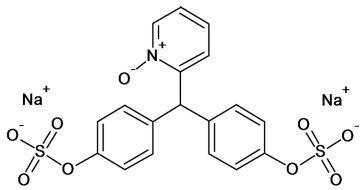
Picosulfate Impurity-8
Molecular Formula: $C_{12}H_{11}NO$
Formula Weight: 185.22



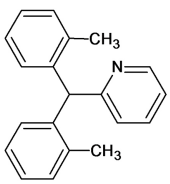
Picosulfate Impurity-9
Molecular Formula: $C_{18}H_{15}NO_3$
Formula Weight: 293.31



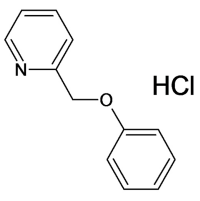
Picosulfate Impurity-10
Molecular Formula: $C_{18}H_{14}NNaO_6S$
Formula Weight: 395.36



Picosulfate Impurity-11
Molecular Formula: $C_{18}H_{13}NNa_2O_9S_2$
Formula Weight: 497.40

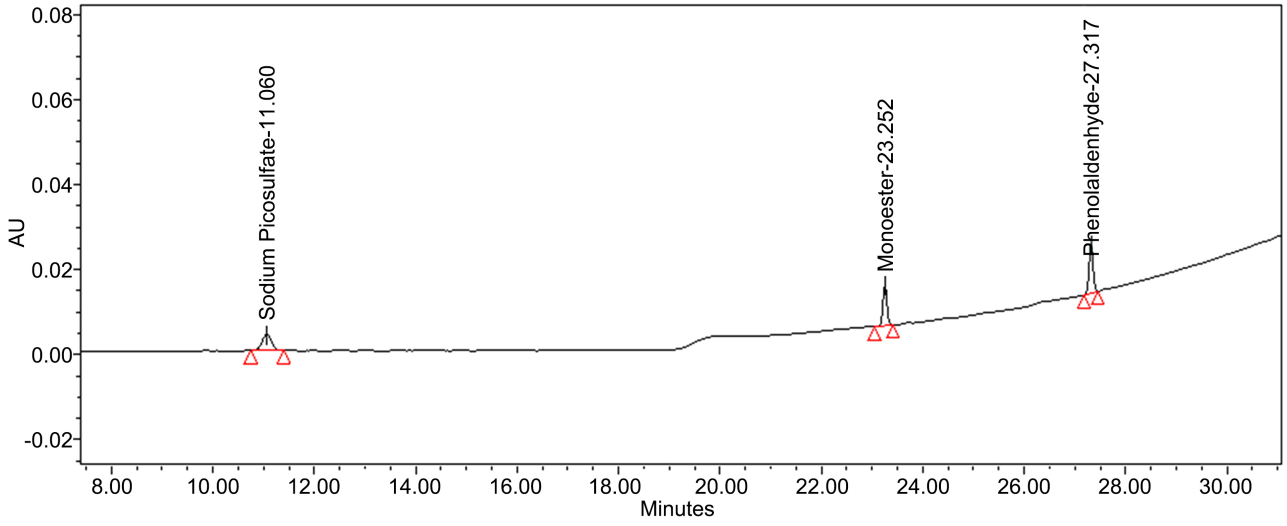


Picosulfate Impurity-12
Molecular Formula: $C_{18}H_{15}NO_2$
Formula Weight: 277.31

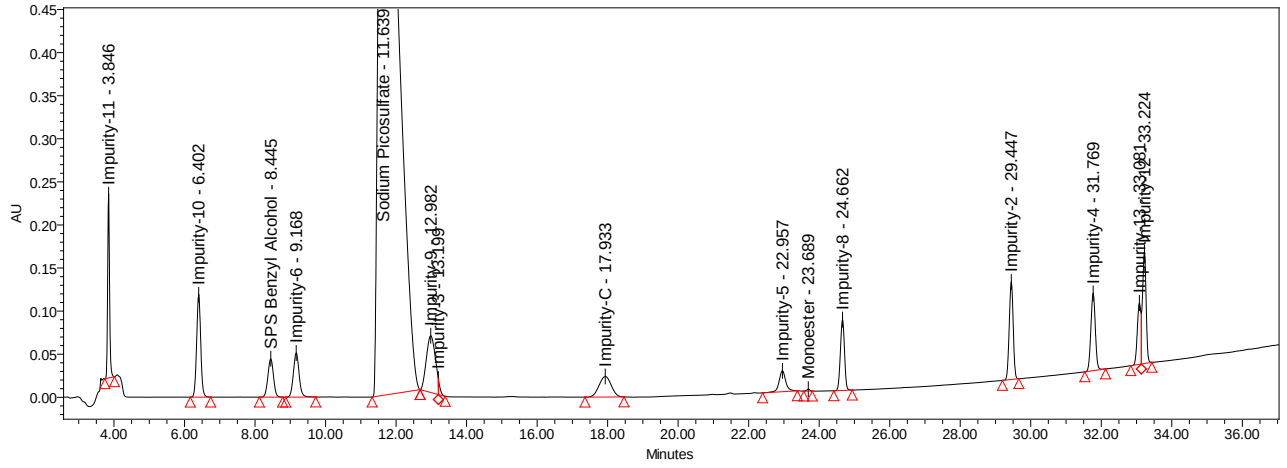


Picosulfate Impurity-13
Molecular Formula: $C_{12}H_{12}ClNO$
Formula Weight: 221.682

Figure 1. Chemical structures of the sodium picosulfate and impurities.



(a)



(b)

Figure 2. (a) System suitability chromatogram; (b) Impurity spiked sample chromatogram.

3. Chromatographic Conditions

HPLC analysis was performed for impurity identification, forced degradation studies and stability analysis of drug substance Sodium Picosulfate. All the chromatographic conditions utilized are described below.

HPLC Chromatographic Conditions

HPLC (PDA Detector with empower software, Waters Corporation, Milford, USA) was used for the analysis and forced degradation and stability testing studies for Sodium Picosulfate. The chromatographic column used was Hypersil BDS C_{18} 5.0 µm, 4.6 × 250 mm, Manufacturer: Thermo Scientific, P/N: 28105-254630. The separation was achieved on a gradient method. 0.01 M of Disodium hydrogen phosphate and 0.01 M of potassium phosphate monobasic buffer and 1 mL of triethyl amine in 1000 mL water adjusted to pH 7.5 with 10% phosphoric acid. Acetonitrile was used as a mobile phase B. The HPLC gradient

program was set as Time (min)/% solution B: 0.0/15, 15.0/15, 30.0/50, 35.0/60, 40.0/60, 42.0/15, 50.0/15. The column temperature was maintained at 35˚C ± 2˚C and the injection volume was 60 µL. Milli-Q water was used as diluent. The mobile phase was pumped at 0.9 mL/min^{-1}. The eluted compounds were monitored at 220 nm. The run time was 50.0 min.

4. Degradation of Sodium Picosulfate

Stress degradation studies of Sodium Picosulfate were performed under ICH recommended acidic, basic, thermal, and UV and visible conditions [14]. For hydrolysis samples stressed under acid and base conditions, the each sample solution was neutralized with acid or base before dilution. Samples were analyzed using HPLC method. The retention time and relative RRT of impurities are mentioned in Table 1. Control sample was injected and the percent degradants were compared against the control sample.

Table 1. Forced degradation data of the sodium picosulfate under various conditions.

Name of the Impurity	RT	RRT	Control sample	1% H_2O_2/ RT/ 60 min	1% H_2O_2/ 60˚C/ 90 min	3% H_2O_2/ 60˚C/ 90 min	6% H_2O_2/ 60˚C/ 120 min	10% H_2O_2/ 60˚C/ 120 min	API Thermal/ 80˚C/ 24 Hours	API-Heat Hydrolysis/ 60˚C/24 Hrs	API-UV Light 48 Hours	API-Visible Light 168 Hours	1 N HCl RT 1 Hr	5.0 N NaOH/ 60˚C/24 Hrs
Picosulfate EP Impurity C Disodium Salt	17.4	1.51	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Sodium Picosulfate Benzyl Alcohol	8.6	0.73	0.03	0.03	0.250	1.077	2.127	2.440	0.03	0.03	0.02	0.03	0.03	0.03
Picosulfate Impurity 2	29.6	2.57	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Picosulfate Impurity 3	13.3	1.16	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Picosulfate Impurity 4	32.0	2.78	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Picosulfate Impurity 5	23.2	2.02	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Picosulfate Impurity 6	9.4	0.82	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Picosulfate Impurity 8	24.8	2.16	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Picosulfate Impurity 9	13.0	1.13	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Picosulfate Impurity 10	6.4	0.56	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Picosulfate Impurity 11	3.9	0.32	ND	ND	ND	ND	ND	0.1	ND	ND	ND	ND	ND	ND
Picosulfate Impurity 12	33.3	2.90	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Picosulfate Impurity 13	33.2	2.89	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Sodium Picosulfate EP Impurity A (Monoester)	23.6	2.00	0.04	0.076	0.246	0.477	0.493	0.493	0.06	0.04	0.08	0.05	0.10	0.05
Sodium Picosulfate EP Impurity B (Phenolaldehyde)	27.5	2.39	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

4.1. Control Sample Preparation

Stock sample of the Sodium Picosulfate was prepared by weighing about 31.25 mg of API into 500 mL volumetric flask. Added water to about 3/4th volume of the flask, sonicated to dissolve. Mixed well and diluted to volume with water. 20.0 mL of above API stock preparation pipetted into 50 mL volumetric flask and injected to HPLC. Control sample was freshly prepared at the time of analysis of other forced degradation conditions.

4.2. Acid Degradation

Stock sample of the Sodium Picosulfate was prepared by weighing about 31.25 mg of API into 500 mL volumetric flask. Diluent (water) was added to about 3/4th volume of the flask, then sonicated to dissolve. The contents were diluted to volume with water and mixed well. 20.0 mL of above API stock preparation was pipetted into 50 mL volumetric flask. The solution was added 0.5 mL of 1.0 N Hydrochloric acid into the same volumetric flask and mixed well. Further, the sample was stressed at room temperature for about 1hour. After 1 hour, The sample was neutralized with 0.5 mL of 1.0 N Sodium hydroxide solution. The sample solution was injected in HPLC.

4.3. Base Degradation

Stock sample of the Sodium Picosulfate was prepared by weighing about 31.25 mg of API into 500 mL volumetric flask. Diluent (water) added to about 3/4th volume of the flask, sonicated to dissolve. The contents were diluted to volume with water and mixed well. 20.0 mL of above API stock preparation pipetted into 50 mL volumetric flask. The solution was added 0.5 mL of 5.0 N Sodium hydroxide into the same volumetric flask. Sample solution stressed in water bath maintained at 60˚C for about 24 hours. After 24 hours, sample was removed from water bath and allowed to reach room temperature. The sample was neutralized with 0.5 mL of 5.0 N Hydrochloric acid solution. The sample solution was injected to HPLC.

4.4. Peroxide Degradation

Stock sample of the Sodium Picosulfate was prepared by weighing about 31.25 mg of API into 500 mL volumetric flask. Diluent (water) added to about 3/4th volume of the flask, sonicated to dissolve. The contents were diluted to volume with water and mixed well. 20.0 mL of above API stock preparation pipetted into 50 mL volumetric flask. Pipetted 1.0 mL of 1% Hydrogen Peroxide solution into the same volumetric flask. Mixed well the solution. The sample was stressed in water bath maintained at 60˚C for about 90 min and removed allowed to reach room temperature and injected to HPLC. Further series of oxidative degradations were performed using 3% H_2O_2/60˚C/90 min, 6% H_2O_2/60˚C/2 hrs and 10% H_2O_2/60˚C/2 hr, 1% H_2O_2/Room Temperature/1 hrs.

4.5. Thermal Degradation

Stock sample of the Sodium Picosulfate was prepared by weighing about 31.25 mg of API into 500 mL volumetric flask. Diluent (water) added to about 3/4th volume of the flask, sonicated to dissolve. The contents were diluted to volume with water and mixed well. 20.0 mL of above API stock preparation pipetted into 50 mL volumetric flask. The sample was stressed in an oven maintained at 80˚C for about 24 hours. After 24 hours and removed from the condition, allowed to reach room temperature and injected to HPLC.

4.6. Photolytic Degradation

4.6.1. API Sample Preparation (UV Light)

Stock sample of the Sodium Picosulfate was prepared by weighing about 31.25 mg of API into 500 mL volumetric flask. Diluent (water) added to about 3/4th volume of the flask, sonicated to dissolve. The contents were diluted to volume with water and mixed well. 20.0 mL of above API stock preparation pipetted into 50 mL volumetric flask. Samples were kept in the photo stability chamber at 4.63 w/m^2 to achieve ICH conditions under UV light for about 2 days. The flask was removed from the photo stability chamber after about 2 days and allowed to reach room temperature and injected HPLC.

4.6.2. API Sample Preparation (Visible Light)

Stock sample of the Sodium Picosulfate was prepared by weighing about 31.25 mg of API into 500 mL volumetric flask. Diluent (water) added to about 3/4th volume of the flask, sonicated to dissolve. The contents were diluted to volume with water and mixed well. Pipetted 20.0 mL of API Stock sample solution into 50 mL volumetric flask. Sample was kept in the photo stability chamber under visible light at 7.19 EU/Lux for about 7 days the flask was removed from the photo stability chamber after about 7 days and allowed to reach room temperature and injected HPLC.

4.7. Water Hydrolysis

Stock sample of the Sodium Picosulfate was prepared by weighing about 31.25 mg of API into 500 mL volumetric flask. Diluent (water) added to about 3/4th volume of the flask, sonicated to dissolve. The contents were diluted to volume with water and mixed well. 20.0 mL of above API stock preparation pipetted into 50 mL volumetric flask. Sample was kept the flask in water bath maintained at 60˚C for about 24 hours. After 24 hours, removed flask from water bath and allowed to reach room temperature and injected to HPLC.

5. Results and Discussion

The forced degradation data generated was compared against the listed impurities and the representative chromatograms were depicted from [**Figure 3** to **Figure 10**] along with the percent impurities in **Table 1**. All the figures [**Figure**

1 to Figure 10, Figure 11] represented with x-axis "Time (min)", and the y-axis "Relative Intensity (a.u.)". The major degradation was observed in the oxidative conditions of the sodium Picosulfate. Sodium Picosulfate is prone to oxidative degradation and the major impurity formed was Sodium Picosulfate Benzyl alcohol impurity [Figure 12]. The remaining all impurities were found to be generated not at significant levels in the drug substance degradation. There were three N oxides structurally possible for the sodium Picosulfate that could arise from oxidative degradation conditions. Forced degradation conditions revealed only one oxidative degradation of N oxide that can generate during the degradation. The oxidative degradation of N oxide could arise from the monoester, phenoldehyde or sodium Picosulfate. As phenoldehyde and monoester impurities are well controlled as process related impurities during the synthetic process the formation of the respective N oxides was relatively not possible. Forced degradation studies also confirmed that there is no formation of monoester N oxide and Phenoldehyde N oxide (Picosulfate Impurity 9 & Picosulfate Impurity 10) [Figure 1].

Sodium Picosulfate shows two absorption maxima *i.e.*, at 220 nm and 263 nm. The analytical method was developed and validated at the wavelength 220 nm due to its primary maximum absorbance at this wavelength. All the known and unknown impurities were detected at this wavelength. However, as an attempt to check any further degradants the secondary wavelength of the Sodium Picosulfate at 263 nm was evaluated. During the review, one unknown @ RRT 0.54 was observed at 263 nm. The unknown @ RRT 0.54 (RT 6.1 mins) was observed in peroxide forced degradation samples with very minimal levels. The same unknown impurity was also seen in the individual impurity injection of Sodium Picosulfate Benzyl Alcohol Impurity. As Benzyl Alcohol Impurity is the oxidative degradant of the Sodium Picosulfate, the unknown impurity was suspected to be the oxidative degradant where the absorption maxima was at 263 nm. The same peak was checked for in the forced degradation study and it was observed in the peroxide degradation of the API indicating that it could be oxidative impurity. The chromatograms depicting the Benzyl Alcohol Impurity is presented

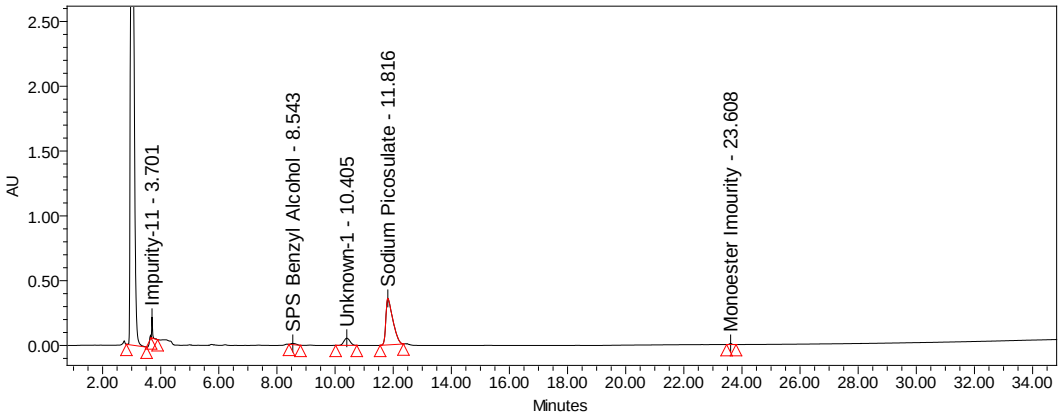


Figure 3. API Peroxide degradation_10% H_2O_2_60˚C_120 MIN.

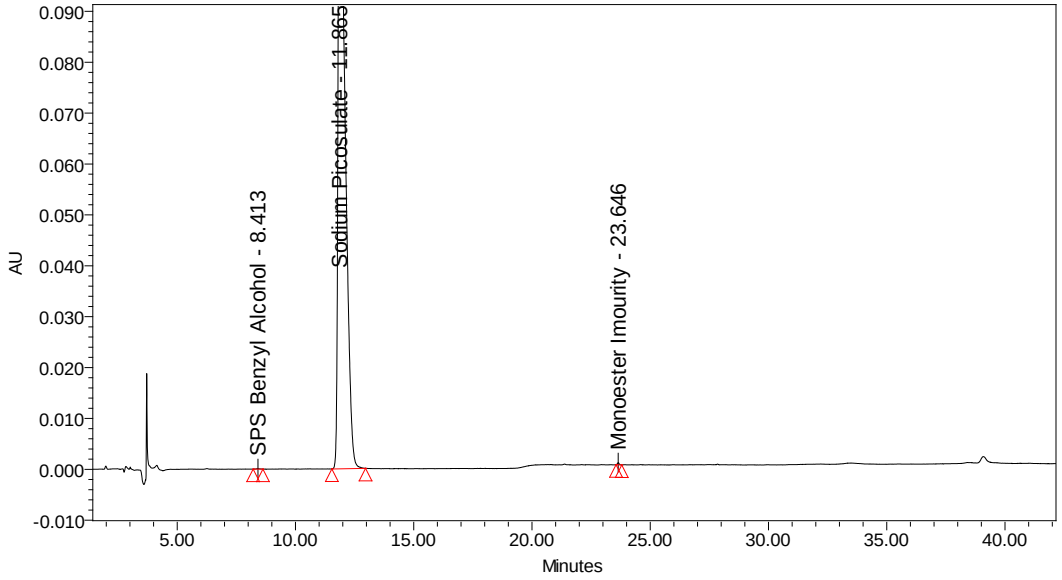


Figure 4. API_Thermal degradation_80˚C_24 hour.

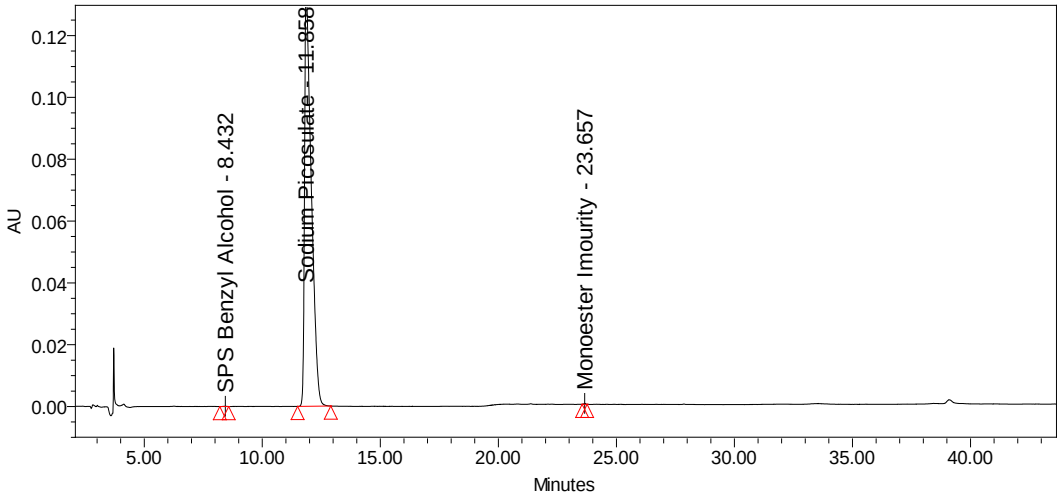


Figure 5. API_Water hydrolysis_60˚C_24 hour.

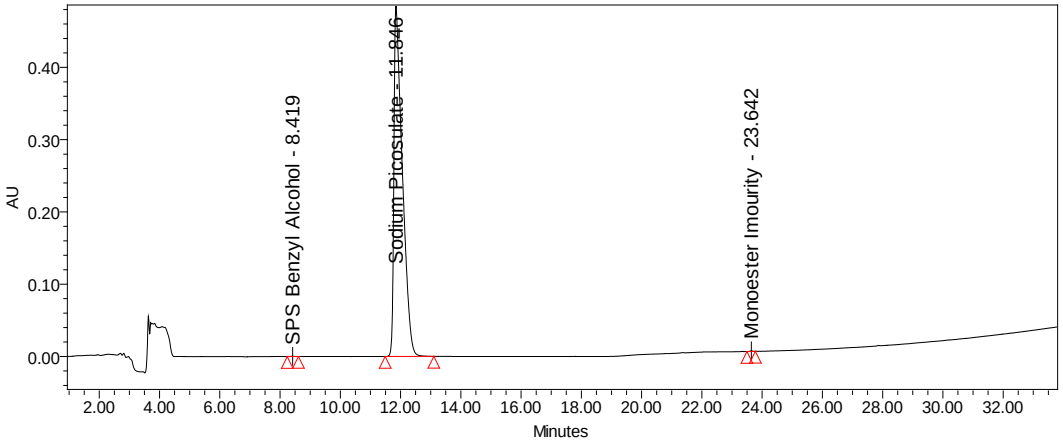


Figure 6. API_Base degradation_5N NaOH_60˚C_24 hour.

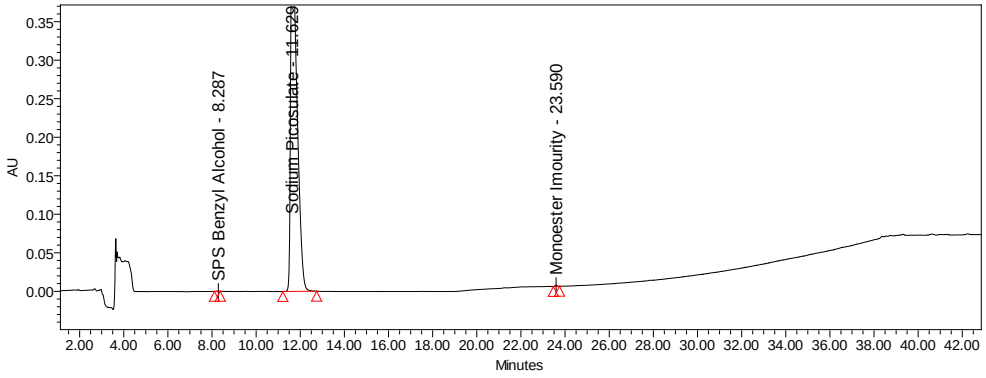


Figure 7. API_Photolytic Degradation_UV_48 Hours.

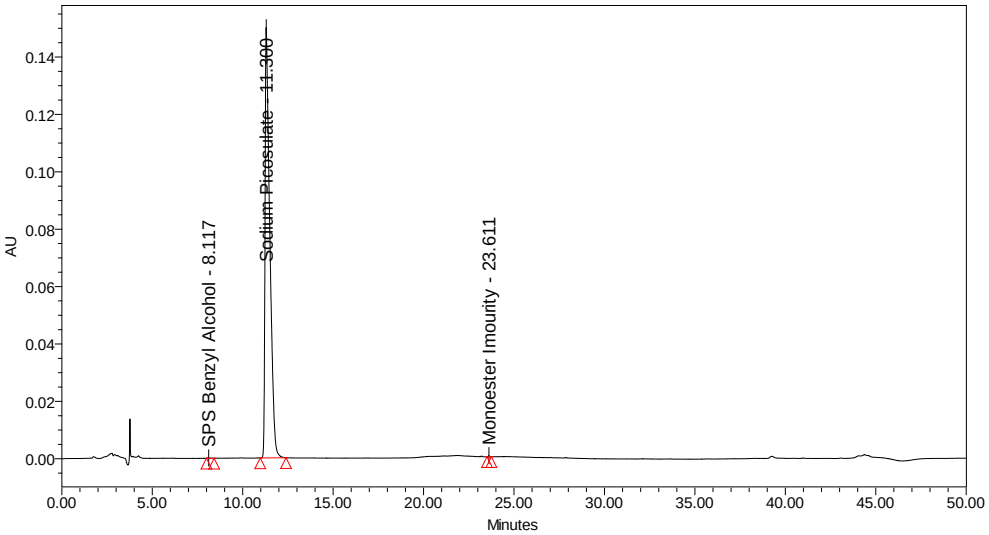


Figure 8. API_photolytic degradation_visible_168 hours.

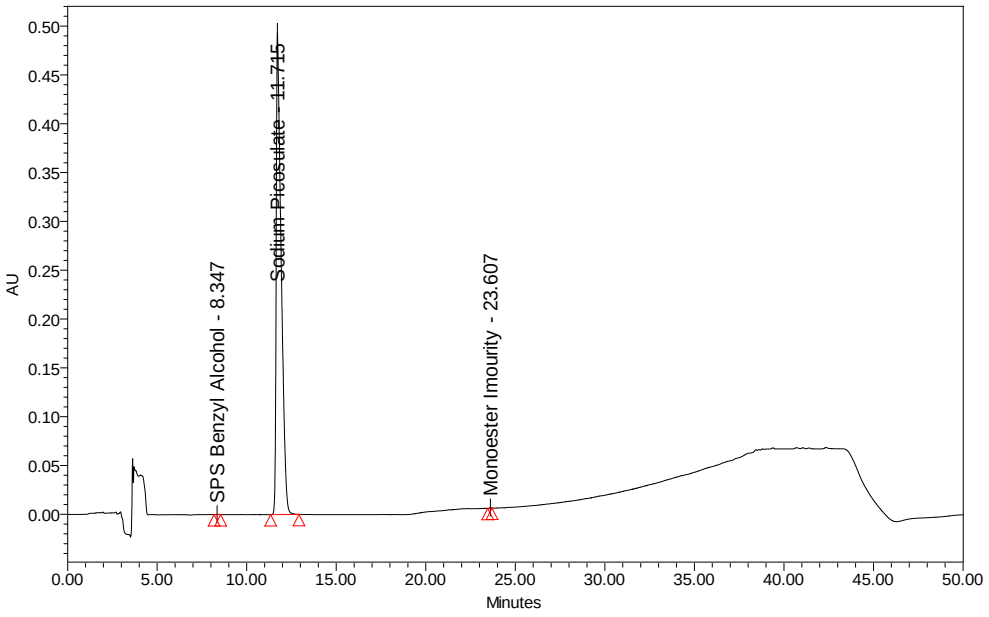


Figure 9. API_control sample.

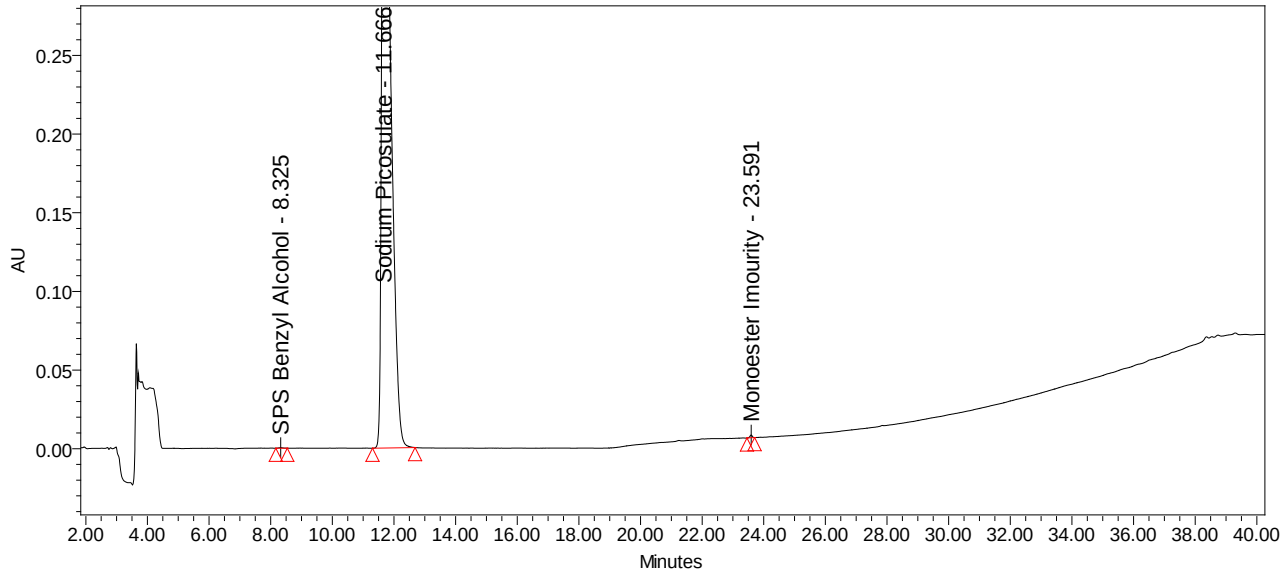


Figure 10. API_acid degradation_1.0N HCl_1 hour_R.T.

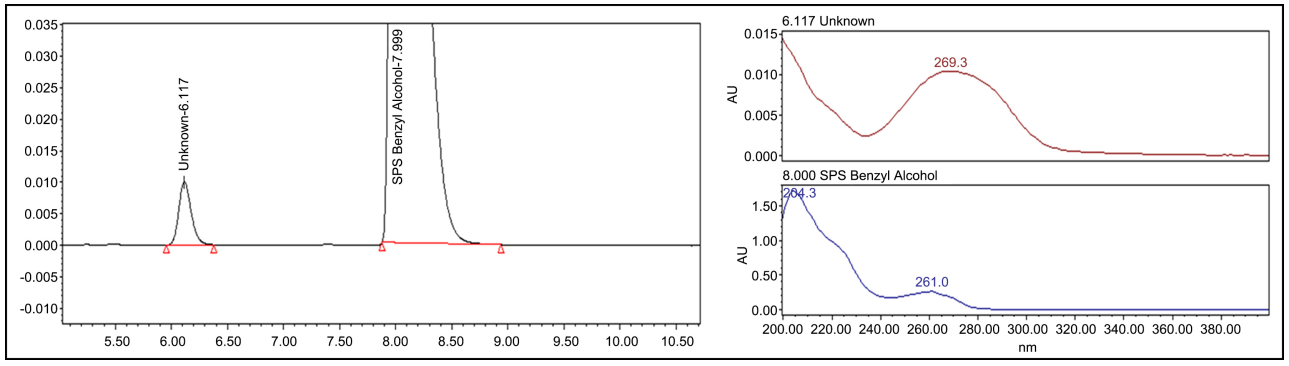


Figure 11. Unknown impurity at RT 6.117 (0.51 RRT) spectra.

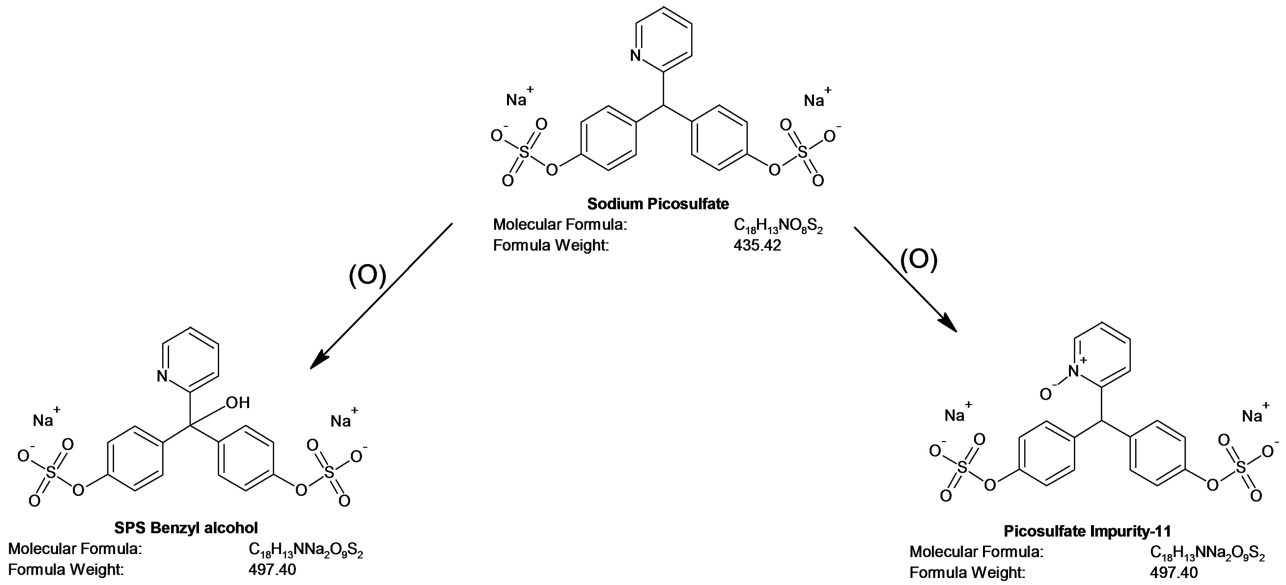


Figure 12. Oxidative degradants of sodium picosulfate.

in Figure 12. As this impurity was observed at low levels, further structural elucidation was not performed. Sodium Picosulfate is prone to oxidative degradation and the major impurities were sodium Picosulfate benzyl alcohol and monoester impurity.

6. Conclusion

In this study, forced degradation behavior of Sodium Picosulfate is explained in detail and all the degradants generated under different stress conditions are reported. The degradant impurities were detected by an HPLC method at two different wavelengths. Sodium Picosulfate was found to degrade in oxidative condition but no significant impurities or degradation products were generated under acidic, basic, thermal or photolytic conditions. This analytical methodology considered as a starting point for the quantification of the sodium Picosulfate in drug product formulations. Further forced degradation studies recommended for the drug product formulation evaluation to understand the degradation characteristics.

Acknowledgements

The authors wish to thank the management of Lupin Somerset for providing the infrastructure for supporting this research work. Cooperation from colleagues Product Development, Quality Control and Analytical Research & Development of Lupin Somerset is appreciated. The opinions expressed in this publication are those of the authors. They do not purport to reflect the opinions or views of the Lupin Somerset or its members. The designations employed in this publication and the presentation of material therein do not imply the expression of any opinion whatsoever on the part of the Lupin concerning the legal status of any country, area or territory or of its authorities, or concerning the delimitation of its frontiers.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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