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Selectivity of Omeprazole Sulphide Oxidation with Cumene Hydrogen Peroxide in Presence of Titanium Isopropoxide and Diethyl Tartrate Complex

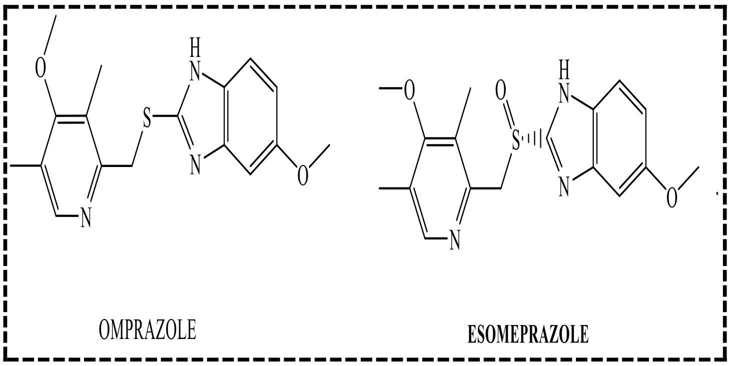
Srikanth Reddy Jonnala
Department of Research and Development
Lee Pharma Limited
Visakhapatnam, Andhra Pradesh, India

Abstract - The Industrial Method of Esomeprazole Synthesis is Sensitive Procedure. The reaction is completely based on Formation of Chiral Complex with Combination of Titanium Isopropoxide + Diethyl Tartrate. This Reaction is Temperature Sensitive and requires Strict Control of reaction conditions to avoid Over Oxidation, racemization and Formation of isomeric impurities. If we Fluctuate any small Temperature variation it may affect the Uncontrolled reaction or more formation of Isomeric Impurities. If Racemization forms During complex, it is the Indication of our complex is instable. Therefore, proper control of reaction parameters is essential for achieving better Yield and product chiral purity. The Present Study indicated the importance of maintaining optimum conditions during the Synthesis process to ensure the stability of the complex and to improve the overall quality of the Esomeprazole production.

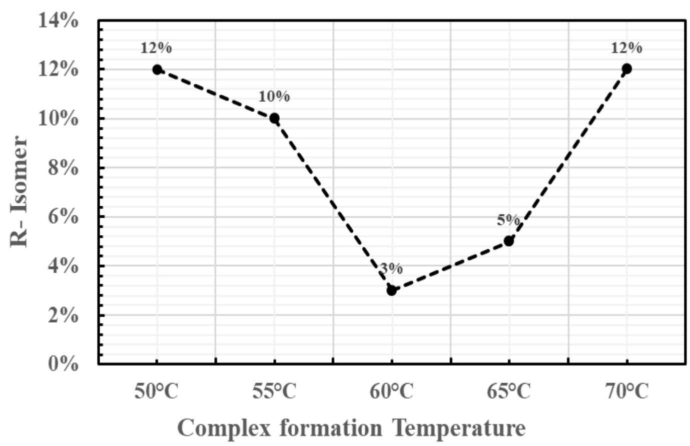
Keywords*: Oxidation, Racemization, Complex, Chiral, Isomer*

I. INTRODUCTION

Esomeprazole is the S-enantiomer of omeprazole and is widely used as a proton pump inhibitor for the treatment of acid-related gastrointestinal disorders. The key step in its asymmetric synthesis involves the formation of a chiral titanium complex using titanium isopropoxide (TTIP) and diethyl tartrate (DET). This chiral complex plays a crucial role in achieving high stereoselectivity and ensuring the preferential formation of the desired S-isomer. The stability of the chiral complex is highly dependent on the reaction temperature during titanium isopropoxide charging. Experimental observations indicated that when the complex formation was carried out at relatively higher temperatures (69.1°C, 69.4°C, and 68.6°C), temperature fluctuations promoted partial racemization, resulting in an uncontrolled reaction and increased formation of the undesired isomer. Under these conditions, the isomeric impurity levels increased to 11.56%, 12.01%, and 10.15%, respectively, indicating instability of the chiral complex. In contrast, conducting the complex formation at lower temperatures (65.1°C, 64.2°C, and 63.6°C) significantly improved the stability of the chiral complex. These conditions minimized racemization, provided better control over the reaction, and enhanced stereoselectivity toward the desired S-isomer. The results demonstrate that maintaining a lower and well-controlled reaction temperature during chiral complex formation is essential for achieving a robust, reproducible, and efficient manufacturing process for Esomeprazole.



This directly Deals for Temperature Influence plays a major Role to Form a proper Chiral Complex During Titanium isoproxide Charging at Recommended Temperatures is 60-65°C. One More Discussion is about presence of base as (*N*,*N*-diisopropylethanamine).The role of *N*,*N*-diisopropylethanamine plays a Crucial role in this reaction [2] by ususage such as triethylamine, 4-methylmorpholine, of other amines resulted in sharp decrease of the optical purity of the product [2]. We found that aromatic N,N-diethyl aniline as a base gives rise to a complex mixture of products



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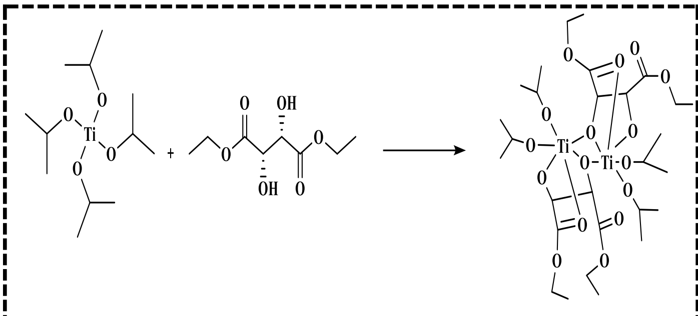
Thus the amine structure strongly affects both reaction direction and product purity. From a manufacturing perspective, the synthesis of esomeprazole presents a significant challenge because it requires high enantioselectivity during the oxidation of omeprazole sulfide to the corresponding sulfoxide[1].



The formation of the desired S-isomer must be achieved while minimizing production of the undesired R-isomer, since enantiomeric purity is a critical quality attribute that directly influences In addition to ensuring high quality, cost-effectiveness, and productivity, it is highly desirable to develop environmentally friendly manufacturing methods In this paper, we report our efforts to enhance production efficiency and develop a robust manufacturing method for high-quality esomeprazole magnesium trihydrate as an API[1].

2. Literature Review:

The Present Study investigates the Influence of using titanium isopropoxide (TTIP) and diethyl tartrate (DET) Chiral complex formation Temperature and amine base selection during oxidation of Omeprazole sulphide. Among all these parameters temperature and mixing pattern plays a particularly important role in formation and stability of the TTIP–DET chiral complex [2]. Development of efficient and scalable methods for the synthesis of optically active sulfoxides has been an important area of pharmaceutical process chemistry because many therapeutically important drugs possess chiral sulfur centers. Among these compounds, esomeprazole, the optically pure (S)-enantiomer of omeprazole, has attracted considerable attention owing to its superior pharmacokinetic profile and improved therapeutic efficacy compared with racemic omeprazole [3]. Consequently, significant efforts have been directed toward developing asymmetric oxidation processes capable of producing esomeprazole with high chemical and optical purity [1].

The earliest manufacturing approaches relied on the preparation of racemic omeprazole followed by optical resolution. Although these methods produced the desired S-enantiomer, they suffered from poor atom economy, additional purification steps, increased solvent consumption, and lower overall process efficiency. These limitations motivated the development of catalytic asymmetric oxidation methods that directly convert omeprazole sulfide into esomeprazole with high enantiomeric excess.

A major breakthrough was achieved with the introduction of titanium-mediated asymmetric oxidation using titanium isopropoxide (TTIP), (S,S)-diethyl tartrate (DET), water, and cumene hydroperoxide (CHP). This catalytic system generates an in situ chiral titanium complex that selectively transfers oxygen to the prochiral sulfur atom of omeprazole sulfide[4], producing esomeprazole with excellent enantioselectivity. The process has become one of the most widely adopted industrial routes because of its scalability, high yield, and reproducible stereochemical control [1].

Mechanistic investigations have demonstrated that the stereochemical outcome depends strongly on the structure and stability of the titanium–tartrate complex [2]. The coordinated chiral catalyst creates a well-defined transition state that directs oxygen transfer to one face of the sulfide substrate, thereby favoring formation of the desired S-enantiomer [5]. Any disturbance of this organized catalytic environment may reduce stereoselectivity and increase the formation of the undesired R-isomer.

Several researchers have reported that reaction variables such as catalyst preparation, reaction temperature, moisture content, reagent addition sequence, solvent composition, and oxidant concentration significantly influence catalyst performance [4]. Among these parameters, temperature plays a particularly important role because it governs the formation and stability of the TTIP–DET chiral complex [2]. Elevated temperatures may accelerate ligand exchange, reduce catalyst rigidity, and promote competing oxidation pathways, ultimately decreasing optical purity and increasing process-related impurities.

The influence of the amine base has also been recognized as an important factor in asymmetric oxidation. N,N-Diisopropylethylamine (DIPEA) has been widely employed because it provides high enantioselectivity and efficient reaction control [1]. In contrast, the use of alternative amines such as triethylamine, 4-methylmorpholine, or aromatic amines has been reported to reduce optical purity or produce complex impurity profiles. These observations indicate that both the steric hindrance and electronic characteristics of the amine significantly influence catalyst stability, substrate activation, and reaction selectivity [7].

The Present paper investigates the Influence of titanium isopropoxide (TTIP) and diethyl tartrate (DET) Chiral complex formation. It is Completely Based on Temperature and Mixing pattern as these parameters play a critical role in determining the stereoselectivity and impurity profile of the reaction. The oxidation reaction was carried out using Cumene hydroperoxide (CHP) as the oxidizing agent. During the addition of CHP, the oxidation reaction is highly exothermic, resulting in the generation of significant heat. If this heat is not effectively removed, localized temperature is increases. In this Context the TTIP–DET chiral complex, promote moisture-related side effects, and increase the formation of undesired R-isomer and sulphide impurities. Therefore, the reaction should be maintained under dry conditions and with efficient cooling to preserve catalyst performance and stereoselectivity.

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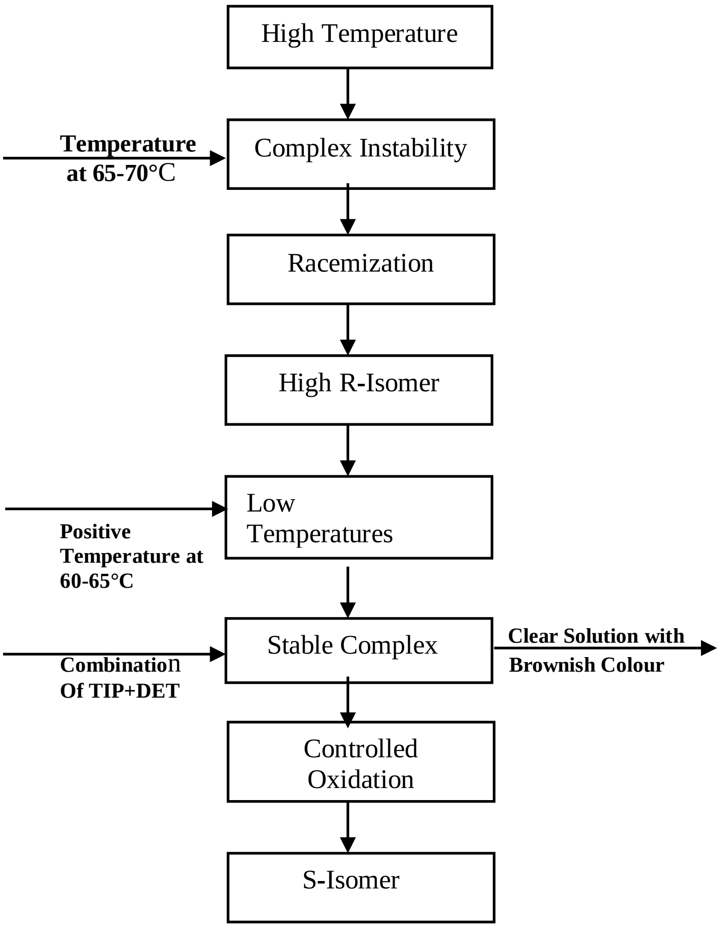
Fig.1 Demonstrates the Complex Pattern

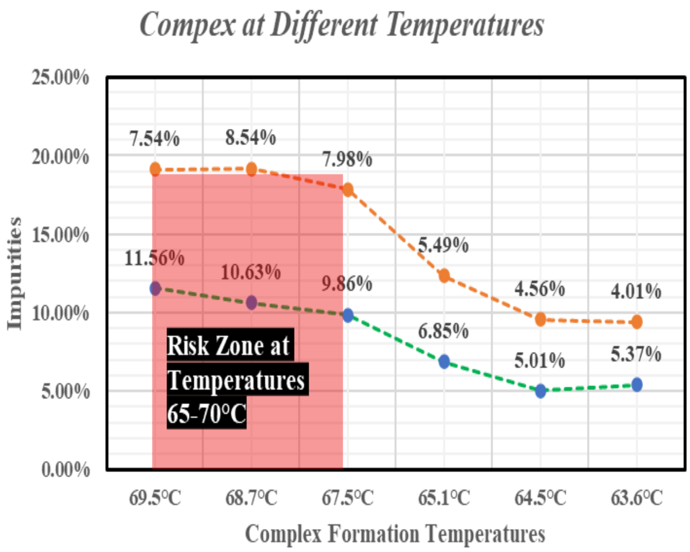


3. Results:

The Influence of Titanium(iv) Isopropoxide (TTIP) and diethyl tartrate (DET) Chiral complex formation. It is Completely Based on Temperature and Mixing pattern as these parameters play a critical role in determining the stereoselectivity and impurity profile of the reaction.

Case-1		
Temperature	**Result**	
69.2°C	Isomer	11.01%
	Sulphide	9.56%
Case-2		
Temperature	**Result**	
68.6°C	Isomer	10.52%
	Sulphide	8.26%
Case-3		
Temperature	**Result**	
67.9°C	Isomer	9.01%
	Sulphide	6.86%
Case-4		
Temperature	**Result**	
65.3°C	Isomer	6.52%
	Sulphide	4.67%

Case-5		
Temperature	**Result**	
64.5°C	Isomer	5.07%
	Sulphide	3.99%
Case-6		
Temperature	**Result**	
63.8°C	Isomer	5.56%
	Sulphide	4.78%



4. Conclusion:

The present study demonstrates that the formation and stability of the titanium tetraisopropoxide (TTIP)–diethyl tartrate (DET) chiral complex are highly dependent on reaction temperature during the asymmetric oxidation of omeprazole sulfide to esomeprazole. Experimental observations showed that maintaining the complex formation temperature within the optimized range of 60–65°C produced a stable chiral catalyst, resulting in improved stereoselectivity, reduced racemization, and lower levels of R-isomer and sulphide impurities.

In contrast, complex formation at elevated temperatures (above 67°C) resulted in catalyst instability, reduced enantioselectivity, and a significant increase in process-related impurities. The results clearly indicate that uncontrolled temperature fluctuations during TTIP charging and the exothermic addition of cumene hydroperoxide adversely affect the reaction by promoting impurity formation and reducing product quality.

The study also emphasizes the importance of efficient mixing, controlled oxidant addition, continuous heat removal, and maintaining anhydrous reaction conditions to preserve the integrity of the TTIP–DET chiral complex throughout the oxidation process. Together, these parameters contribute to a robust, reproducible, and scalable manufacturing process capable of consistently producing esomeprazole with high chemical purity, excellent optical purity, and improved process efficiency.

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