PREFACE

This academic journey has been long but it was an enriching experience for me. My research interest has taken me to the challenge of combating the evil of drug resistance through enhanced production of a crucial modern-day anti-MRSA antibiotic, "Daptomycin" and the improvement of its efficacy as a combinatorial drug with nanoparticles. The constant urge to fight drug resistance has led to new developments in healthcare industries. There has been an alarming situation as antibiotic resistance has become a serious clinical issue. The armory of antibiotics has very few dependable replacements. The healthcare sector is intimidated by the labor and costs of putting an entirely new molecule in the market which are otherwise, unresponsive towards the conventional antibiotics. Daptomycin has gained prominence as a novel antibiotic produced by *Streptomyces roseosporus* which has demonstrated a broad spectrum of activity in vitro against a wide range of aerobic and anaerobic gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant Enterococci. Drug resistance is a global threat to human health in today's era. Several conventional and non-conventional antibiotics have become inefficient to tackle this problem. Daptomycin is a potential cyclic-lipopeptide antibiotic produced by *Streptomyces roseosporus.* It has progressed as a significant anti-MRSA (methicillin-resistant *Staphylococcus aureus*) antibiotic. But, the applicability of this highly valued antibiotic is hampered by its low production and stringent processing methodology. The current perspective on bioprocess intensification for Daptomycin production would draw the attention towards the incredible potentialities of this life saving drug and the strategies to improve its production. The aim of this study is to develop various strategies to ameliorate

the production of Daptomycin through various cell processing strategies using different modes of bioreactors and to enhance the potency of Daptomycin against drug resistant species through its synergy with noble metal nanoparticles.

The first phase of the work was concerned with the optimization of process parameters for enhanced Daptomycin production by *Streptomyces roseosporus* using one-factor-at-a-time OFAT method and Taguchi statistical analysis method.

The second phase of the work involved the evaluation of rheological properties of the fermentation broth which is a serious concern in process intensification of Daptomycin.

The third phase of the work dealt with the production of Daptomycin using different modes of bioreactors using various cell processing strategies.

The fourth phase of the work was concerned with the mass transfer studies of the fermentation broth using different spargers.

The last phase of the work dealt with the application of Daptomycin against MRSA using its synergistic effect with noble metal nanoparticles in the form of topical gel.

The work incorporated in the present thesis has been arranged in five chapters. The first chapter contains the general introduction of the subject, its structure and importance. This chapter throws light on the importance of Daptomycin as an anti-MRSA antibiotic. Biosynthesis, mechanism of action and strategies for its production have also been discussed.

Chapter two provides the exhaustive review of the up-to-date literature published related to the work on the various aspects of history of Daptomycin, the challenge of drug resistance, mode of action of Daptomycin, biosynthesis, metabolic flux and genetic improvement and its applications in healthcare sector. A systematic year wise literature is provided for the better

understanding of the present work. Objectives of the present work have also been included in the chapter.

Chapter three discusses the material and methodology used for the entire study. General experiment set up, media formulations, different assay and protocols used in production studies, topical gel formulation schemes have been described.

The fourth chapter deals with the results obtained during the experiments carried out in the chapter three followed by discussions.

Chapter five summarizes the main findings of the above studies and overall conclusions that were obtained.

At the end, the thesis has been appended by up-to-date list of references. References have been arranged alphabetically according to the surname of the first author.

List of the publications have been attached at the end of the thesis.

In my hope and belief the entire contents of the thesis has been compiled on my research.