PREFACE

"If I have ever made any valuable discoveries, it has been owing more to patient attention, than to any other talent."

- Sir Isaac Newton

A therapeutic compound known as rapamycin drew my attention as it was reported to have several functions including immunosuppression. Costly transplantations followed by post-operation management by life time use of immunosuppressants render huge impact on patients.

Thus, I chose this study to identify some solutions for enhancement of rapamycin production by using a microbial strain of *Streptomyces hygroscopicus*. The strategies were based on different process parameters which could affect the fermentation system.

Firstly, I tried to optimize the medium composition for rapamycin production using statistical analysis. The optimized medium was then used for further studies in shake flask and bioreactor. The kinetic analysis of rapamycin production was carried out in stirred tank bioreactor. Once the kinetic behavior of fermentation process was analyzed, then different strategies were employed to study their effect on rapamycin production.

Cells were immobilized on different pre-treated support materials. This facilitated the re-use of cells for antibiotic production. Moreover, the morphological changes also altered the production pattern due to variation in mass transfer.

Then the production in an Airlift reactor system was studied with higher dissolved oxygen transfer ability. Also, the physical stress conditions were reduced due to impeller free mixing.

Another strategy which was evaluated was effect of stress condition on *Streptomyces* as they produce rapamycin which also acts as an antifungal agent. Thus, the impact of presence of *Candida albicans* in the surroundings of rapamycin was evaluated in shake flask studies.

Finally, an attempt was made to enhance the production of rapamycin by extended stationary phase. This strategy employed the maintenance energy requirement of rapamycin during stationary phase.

In order to validate the production of rapamycin, purification was carried out. The purified sample was then characterized using different analytical techniques.

Thus, with immense support and guidance of my Ph.D. supervisor, Prof. Pradeep Srivastava, I have compiled my efforts in the form of this thesis. The thesis has been divided into five chapters:

1. **Introduction:** Details the importance of rapamycin as a therapeutic agent
2. **Review of Literature:** Describes the studies done so far in the area of bioprocess development of rapamycin and other antibiotics
3. **Materials and Methods:** Provides the information about the chemical reagents and other aids utilized during the study. It also describes the methodologies which have been adopted for the study
4. **Results and Discussion:** Gives an insight into the findings of this study and their implications
5. **Conclusion:** Summarizes the work as well as provides the future scope of this work

List of publications have been attached at the end.

I hope this research report would be interesting for the researchers working in the area of Biochemical and Bioprocess Engineering.