EXPLORING THE ROLE OF BIOCATALYSIS IN PHARMACEUTICAL SYNTHESIS

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ABSTRACT

The use of Biocatalysis as part of a manufacturing process fits well in this trend as enzymes are themselves biodegradable, require mild conditions to work and are highly specific and well suited to carry out complex reactions in a simple way. Advances in molecular biology and bioinformatics, and the decreasing costs for gene synthesis and sequencing contribute to the growing success of engineered biocatalysts in industrial applications. The design and development of greener processes that are safe and friendly is an irreversible trend that is driven by sustainable and economic issues. However, the incorporation of biocatalytic process steps in new or established manufacturing routes is not always straight forward. To realize the full synthetic potential of biocatalysis for the sustainable manufacture of chemical building blocks, it is therefore important to regularly analyze the success factors and existing hurdles for the implementation of enzymes in large scale small molecule synthesis.. The pharmaceutical industry, driven by an increasing need to deliver new and more effective medicines to patients, is increasingly turning to the use of engineered biocatalysts for both lead generation of active compounds and the sustainable manufacture of active pharmaceutical ingredients. Advances in enzyme discovery, high-throughput screening and protein engineering have substantially expanded the available biocatalysts, and consequently, many more synthetic transformations are now possible. This review explores the effective role of NBCs in pharmaceutical and biomedical fields.

Keywords: *Biocatalysis, pharmaceutical, manufacturing process, biomedical fields, immobilization.*

INTRODUCTION

Bio-catalysis is the use of enzymes in chemical synthesis. These enzymes can be used as isolated preparations or in whole cell format, prepared either in their native cells or as recombinantly expressed proteins in alternate host cells. Additionally, biocatalysis offers both economic and environmental advantages over chemocatalytic methods. The significant expansion in biocatalytic implementation in pharma is heavily tied to the ability to evolve enzymes. This is critical for improving the scope of wild-type enzymes toward non-natural substrates and increasing their activity and tolerance to the demanding process parameters needed to make syntheses commercially and environmentally viable. Additionally, the breadth of the biocatalysis toolbox continues to grow as a result of academic developments in the field, key industrial-academic collaborations, and in-house enzyme discovery efforts. Biocatalytic reactions inherently begin to address these challenges as they typically operate in aqueous solvent under mild temperature and atmospheric pressure. However, for biocatalysis to live up to the label of being a sustainable technology, there is also a strong requirement to maintain process intensification metrics that match typical synthetic organic chemistry. One of the more recent capabilities of biocatalysis that has now been implemented on scale is the combination of multiple enzyme-catalyzed steps in one-pot, which avoids the need for time-consuming, material-intensive, and costly isolation procedures.

LITERATURE REVIEW

Russell D. Lewis (2023) Biocatalysis is a highly valued enabling technology for pharmaceutical research and development as it can unlock synthetic routes to complex chiral motifs with unparalleled selectivity and efficiency. This perspective aims to review recent advances in the pharmaceutical implementation of biocatalysis across early and late-stage development with a focus on the implementation of processes for preparative-scale syntheses.

Nango Gaye (2023) Our study focused on the valuation of Tchiky clays. This work aims to evaluate its properties to explore possible uses in pharmacy. Physico-chemical and mineralogical characterizations were carried out, as well as pharmacopoeial tests and an evaluation of the antioxidant activity. Thus, chemical analysis by X-ray fluorescence spectrometry gave silicon (55.65%), iron (15.73%), aluminum (13.53%), potassium (6.05%), titanium (3.98%), magnesium (2.10%), and calcium (0.82%). X-ray diffraction showed the presence of kaolinite, quartz and illite. This study also revealed that the sample studied was essentially a plastic clay of hard consistency, with average flowability. These results should allow use as an excipient in pharmacy, particularly in liquid, semi-liquid and pasty formulations.

Vinod Kumar Nigam (2020) Biocatalysis has been continuously evolving as an essential tool which is playing a significant role in the industrial synthesis of chemicals, active pharmaceuticals, pharmaceutical intermediates, etc. where the high-yielding chemo-, regio-, and enantioselective reactions are needed. Despite its vital importance, industrial biocatalysis is facing certain limitations such as operational stability, economic viability, efficient recovery, and reusability. The limitations mentioned can be overcome by the isolation of specific enzyme producers from extreme environment by protein engineering, bioinformatics, and recombinant DNA technologies. Recently, chemoenzymatic pathway and biological cascade reactions have also been developed and designed to perform the synthesis of pharmaceuticals.

Huihua Sun (2018) Biocatalysis has been increasingly used for pharmaceutical synthesis in an effort to make manufacturing processes greener and more sustainable. Biocatalysts that possess excellent activity, specificity, thermostability and solvent-tolerance are highly sought after to meet the requirements of practical applications. Generating biocatalysts with these specific properties can be achieved by either discovery of novel biocatalysts or protein engineering. Meanwhile, chemoenzymatic routes have also been designed and developed for pharmaceutical synthesis on an industrial scale. This review discusses the recent discoveries, engineering, and applications of biocatalysts for the synthesis of pharmaceuticals and pharmaceutical intermediates.

Matthew D. Truppo (2017) The use of bio-catalysis in the pharmaceutical industry continues to expand as a result of increased access to enzymes and the ability to engineer those enzymes to meet the demands of industrial processes. However, we are still just scratching the surface of potential bio-catalytic applications. The time pressures present in pharmaceutical process development are incompatible with the long lead times required for engineering a suitable biocatalyst. Dramatic increases in the speed of protein engineering are needed to deliver on the ever increasing opportunities for industrial bio-catalytic processes.

The Benefits of Biocatalysis

Biocatalysis is an appealing technology for the pharmaceutical industry for several reasons. Enzyme-based catalysis meets the ever increasing demands for highly selective, safe, and sustainable industrial processes. Unlike their chemocatalyst counterparts, biocatalysts have a very large three-dimensional structure that makes multiple points of contact with a substrate of interest, allowing for exquisite selectivity. Through protein engineering, modifications to the protein sequence and therefore structure can be easily made to change the properties of the biocatalyst. The excellent regio- and stereos electivity of enzyme catalysts along with their ability to work under mild reaction conditions (thus protecting existing functionality within a molecule) enables transformations without the need for multiple protection and deprotection steps within a synthesis.

Scenario of biocatalysis in pharmaceuticals industries and its pertinent applications

In 1992, Roger Sheldon estimated environmental impact factor (E factor) (kg waste/kg product) for several chemical industries, and an E factor of 25–>100 was noted in the pharmaceutical industries. Thus, to reduce the harmful impact of pharmaceutical manufacturing processes and making it more sustainable, "green chemistry" has been increasingly adopted. An efficient biocatalytic process encompasses the "12 principles of green chemistry" to an extent which give it an edge over other technologies

Investigations on Enzyme Synthesis by Efficient Pathways

Research work on green synthesis and enzyme kinetics is summarized respectively. Proteins carry out a variety of functions like transport, storage, support, and antibodies. Proteins also act as an enzyme in many reactions. For enzyme or biocatalyst, selectivity and volume efficiency are very important properties. For the synthesis of glycosides, enzymatic pathways offer a better option by overcoming the limitations of the chemical synthesis method. Immobilization by a suitable method such as adsorption can be very effective for efficiently using enzymes in biochemical reactions. Adamczak and Krishna investigated the improvement of enzymes for efficient biocatalysts. Bio-catalysis has a wide scope in the pharmaceutical and agrochemical industries. Excellent results are obtained by the application of gene encoding for enzymes. Improvement in the activation methods and microbial screening has resulted in novel enzymes resulting in new biocatalysts pathways for different properties. Barbosa et al. investigated lipase immobilization. They used Mesoporous silica as support for the biocatalyst. They observed that when modified by the protic ionic liquid, the yield and operational stability increased. According to this investigation, lipase immobilized into silica aerogel by encapsulation methods showed the best immobilization technique.

Enzymes in the Fine Chemicals Industry

The role of Biocatalysis in the pharmaceutical and fine-chemical industries is clearly expanding. There are estimated to be around 150 implemented biocatalytic processes in industry, and the majority of these are in the pharmaceutical sector. As stereoisomerism is quite relevant in pharmaceutics and fine chemistry, and a single swap in hydrogen position may mean a great difference in the bioactive function of a compound, Biocatalysis fits well to meet these challenges. Besides the enantio-, regio- and chemoselectivity that enzymes exhibit, their ability to perform complex catalysis procedures in a simple step, which otherwise, under a chemical approach, might require laborious treatments, toxic reagents or high energy input, has provided a strong basis for their usage in the fine chemicals industry.

RESEARCH METHODOLOGY

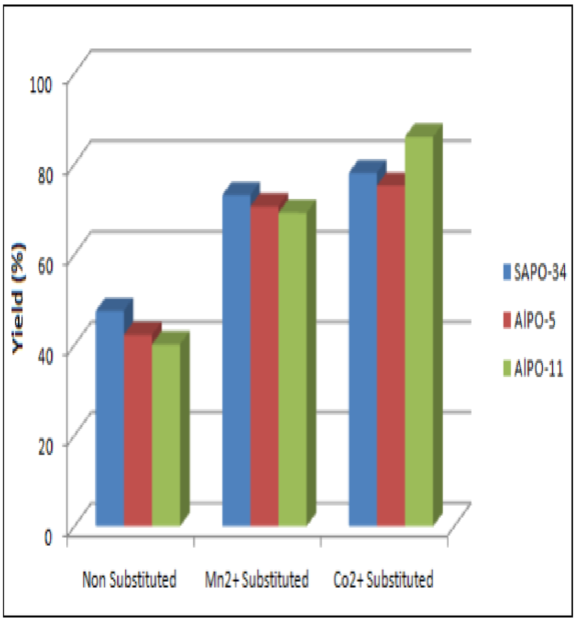
The synthetic polymers have hampered the application of natural polymers in controlled drug delivery systems to deliver the bioactive agents. Natural polymers are offering some advantages over synthetic polymers like unbeatable biocompatibility as made by nature, biodegradability, nontoxicity, property to get decompose in nature, environmental-friendly processing, local availability, conservation of petroleum resources, etc. and most importantly esuriently of living organisms to degrade them. Synthesis of Zeolites by hydrothermal method and Separation of the material with the help of high speed centrifuge. Gas Chromatography (GC) for analysis of the product. Product characterization by GC-MS, NMR, FTIR and XRD analytical technique from patient tolerance as well as public acceptance point of view there is less chances of adverse effects with natural materials compared with synthetic one. Synthesis of organic compound using Zeolite as a catalyst and Separation of by-product by column chromatography. To improve therapeutic efficacy of drugs, the formulation scientists are trying to modify the formulation process, technology, etc. Apart from this, polymeric systems play an important role in modifying drug delivery system. Excipients are the largest components of any pharmaceutical formulation. Their origin may be natural, or synthetic source and synthetic excipients have become commonplace in today's pharmaceutical dosage forms

RESULTS AND DISCUSSIONS

All catalyst materials with their metal analogues, were cyclodehydration of 1, 4-diol. The reaction conditions were followed according to the scheme 1. Effect of different synthesis variables is given in the following table 1 and graph 1. In the reaction which is performed according to the scheme 1, solvent was not taken, much amount of catalyst causes solidification of reaction mixture and reactants do not get mixed properly.

Table 1: Effect of different catalysts on the yield of tetrahydrofuran

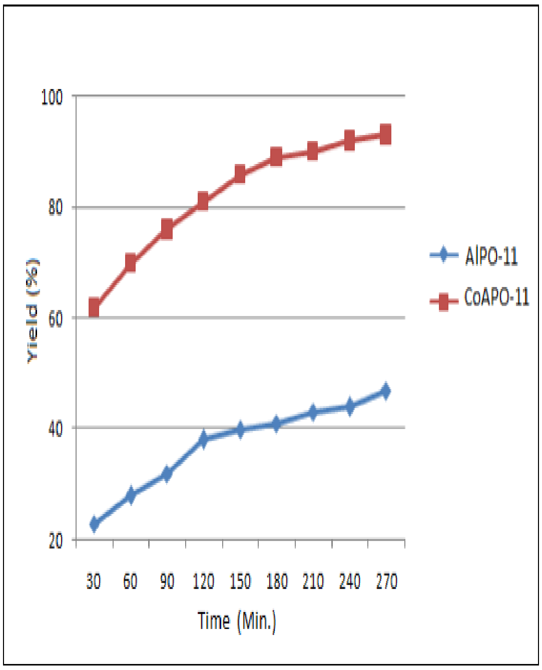
Catalyst form	% yield of catalytic forms		
	SAPO-34	AlPO-5	AlPO-11
Non Substituted	47.53	42.23	40.14
Mn^{2+} Substituted	73.2	70.69	69.27
Co^{2+} Substituted	78.1	75.3	86



Graph 1: Effect of catalysts on the yield of tetrahydrofuran

Effect of reaction time

Reaction time has a great importance from green chemistry point of view and energy consumption. Effect of reaction time on the synthesis of tetrahydrofuran over various catalytic forms of zeotypes was observed with the same reactants following the Scheme 1 and presented in the tables 2 and graphs 2. TLC plate was developed using n-hexane and ethyl acetate as developing solvent in 7:5 ratio. Reaction aliquots were taken at different successive intervals of time and analysed using TLC plate. Reaction was continued till the appearance of single point in the TLC plate.



Graph 2: Effect of reaction time on the yield of tetrahydrofuran over various catalytic forms of AlPO-11

Due to this fact, the amount of catalyst was taken in this range of weight. It is observed that as the amount of catalyst increases, the yield of product also increases but after 100 mg amount of catalyst reaction rate was not increasing in proportional way and also caused impurities due to un-reacted reactants (observed in TLC plate).

Table 3: Effect of weight of catalyst on the yield of tetrahydrofuran over various catalytic forms of AlPO-11

Weight (mg)	% yield of catalytic forms		
	AlPO-11	MnAPO-11	CoAPO-11
50	32.4	39.45	46.12
70	36.87	42.67	48.28
90	45.61	49.71	56.58
110	48.41	52.83	63.38
130	56.75	59.09	68.99
150	65.68	68.35	73.01

CONCLUSION

Biocatalysis has made a remarkable journey so far and has been successfully applied for the numerous biotransformation processes in several industries. It has benefitted nearly all sectors, particularly chemical and pharmaceuticals. Biocatalysis has made a remarkable journey so far and has been successfully applied for the numerous biotransformation processes in several industries. It has benefitted nearly all sectors, particularly chemical and pharmaceuticals. Biocatalysis is currently employed in a number of processes and products in diverse fields, and certainly new areas of application will be added. Advances in computational power have enabled the advent of bioinformatics, genomic sequencing and powerful analytic methods in physics, chemistry and molecular biology, which have allowed us to understand the dynamics, in vivo and in vitro, of biomacromolecules. Biocatalysts can be used for much fermentation, reduction, decomposition, and other reactions. Biocatalyst processes are accepted widely in pharmaceutical and fine chemical synthesis. The application of enzymes has developed from traditional knowledge and experience in various areas towards specialized manufacturing methodologies in industrial sectors such as the food and drink industries, chemical and pharmaceutical industries, agrochemical industry, detergent, household and personal care industries, cosmetics industry, as well as the flavor and fragrance industry. The continued progress and interest in enzymes, serves as stimulus to make further efforts and ensure a steady success in meeting new synthetic challenges.

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