© MAR 2026 | IRE Journals | Volume 9 Issue 9 | ISSN: 2456-8880
DOI: https://doi.org/10.64388/IREV9I9-1715223

Process Development and Intensification of Chemical Reaction

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Abstract- The chemical industries are pivotal to the modern world and works to convert raw materials such as oil painting, natural gas, air, water, essence, and minerals into more than 70,000 different products. These base products are also used to make consumer products in addition to manufacturing, service, construction and other. The process of the organic chemicals by using a zero waste discharge technology and the solvent recovery to make a green reaction, which is economically feasible as well grounded on the conception of waste management by using the different types of catalyst and studying the part catalyst in the reaction. In the upstream reaction an amidation reaction is developed here in the project of the pharmaceutical intermediate or product which is extensively used in chemical and pharmaceuticals. The use of the zero valent palladiumnano catalyst system for amidation of aryl halides which has not been efficiently proved. The reaction is well liberalized toward a variety of functional aryl halides and a wide range of aromatic and aliphatic primary amides in good to excellent yields. Nanoparticles having extraordinarily large surface area and huge number of active sites in comparison to bulk material act as effective catalyst for organic synthesis.

I. INTRODUCTION

Since hundreds of years, a compound similar to paracetamol form of willow bark has been used to relieve pain and to treat fever. Cinchona bark extract was used to produce antimaterial drug quinine. Scientifically it is known as N-acetyl-p-aminophenol and acetaminophen or paracetamol, this drug has become the backbone of modern medicine for the treatment of mild to moderate pain and fever. First synthesized in 1877, it has become the most widely used analgesic and antipyretic drug in the world. Because of safety and efficacy standards it has been included in the World Health Organization's List of Essential Medicines. Although its efficacy in the treatment of fever in children is still a matter of debate. Paracetamol effects occur on ingestion, relaxation, mild drowsiness, feeling tranquility, and euphoria. The side effects can also be seen in other aniline analgesics, such as acetanilide and phenacetin. But due to the long term use of paracetamol it leads to the develop a habit to the patient.

Paracetamol has been used for a long time, yet the mechanism of action isn't completely clear. It's considered one of the most popular analgesic products which are produced with a different type of weak opioids. The effective routes of administration are orally (as tablets) or rectally (as suppositories). The amount of API (active pharmaceutical ingredient) in the oral dosage form usually varies between 500-1000 mg for 4-5 hours which is 4 g in total for a daily dose. The side effects of paracetamol are agranulocytosis and other hypersensitivity reactions. It has no low dose effect but can harm the liver and renal when it's over-dosed. This is due to the accumulation of N-acetylbenzoquinoneimine, (referred to as NABQI). However, paracetamol is not soluble in aqueous solutions and thus it has no parenteral dosage forms [6].

Considering these gaps and recycling of unreacted reactant, Recovery of Solvent, Recovery of Catalyst in Paracetamol Manufacturing also to develop cost effective and ecofriendly process for synthesis of Paracetamol this research was carried out. The synthetic route of a combining p- aminophenol and acetic anhydride used here for the experiment. Also, Raman Spectroscopy with Infrared Spectroscopy used to analyze the synthesized acetaminophen.

II. LITERATURE REVIEW

The study includes the possible impurities that can be formed at the time of synthesis of paracetamol using different synthesis routes. The conventional route uses p-aminophenol as a starting material with acetic anhydride as an acetylating agent producing paracetamol and acetic acid as a side product. This reaction is mostly carried out in three different solvents, viz. isoamyl alcohol, 2-propanol and water.

Sarah M. Crawford, Et al. have proposed the work on Bippy Phos: A Single Ligand with Unprecedented Scope in the Buchwald–Hartwig Amination of (Hetero)aryl Chlorides in this work the development of new ligands for the palladium-catalyzed arylation of amines and related NH-containing substrates were studied. The formation of structurally diverse ligands, has facilitated the accommodation of sterically and electronically divergent substrates including ammonia, hydrazine, amines, etc. Despite these achievements, problems with catalyst generality persist and access to multiple ligands is necessary to accommodate all of these NH-containing substrates. In this quest to address this significant limitation they had identified the BippyPhos/[Pd(cinnamyl)Cl]2 catalyst system as being capable of catalyzing the amination of a variety of functionalized (hetero)aryl chlorides, as well as bromides and tosylates, at moderate to low catalyst loadings. The successful transformations described herein include primary and secondary amines, NH heterocycles, amides, ammonia and hydrazine, thus demonstrating the largest scope in the NH-containing coupling partner reported for a single Pd/ligand catalyst system.

Takashi Ikawa, Et al. have proposed the work on Pd-Catalyzed Amidations of Aryl Chlorides Using Monodentate Biaryl Phosphine Ligands: A Kinetic, Computational, and Synthetic Investigation, present results on amidation of aryl halides, sulfonates using a monodentate biaryl phosphine pd catalyst. The results are in accord with the previous studied reports that suggests that the formation of K^2- amidate complexes is deleterious to the effectiveness of a catalyst for this transformation and that their formation can be prevented by the use of appropriate bidentate ligands, in this report the data suggests that the use of certain monodentate ligands ca also prevent the formation of the k^2 amidate complexes and thereby generate more stable catalysts for the amination of aryl chlorides.

Artis Klapars, Et al. proposed a work on A General and Efficient Copper Catalyst for the Amidation of Aryl Halides in this paper they had developed experimentally simple and inexpensive catalyst system for the amidation of aryl halides by using 0.2 – 10 mol % of CuI, 5-20 mol % of 1,2-diamine ligand and k3po4, k2co3 or cs2co3 as base. Catalyst system based on N,N-dimethylethylenediamine or trans-N,N-dimethyl-1,2- cyclohexanediamine were found to be the most active even though several 1,2 – diamine ligands could be used in easiest cases. Aryl iodides, bromides, and in some cases even aryl chlorides can be efficiently amidated.

Mita Halder, Et al. proposed the work on Biogenic Nano-CuO-Catalyzed Facile C–N Cross-Coupling Reactions: Scope and Mechanism they have demonstrated a green and efficient biogenic synthesis of copper(II) oxide nanoparticles using easily available Ocimum Sanctum leaf extract at room temperature. The biogenic copper oxide nanoparticles have shown excellent activity on N-arylation of cyclic and acyclic amides with aryl and styryl halides. Broad substrate scope, excellent functional group tolerance, and high yields were observed. This protocol is also extended for the N-arylation of substituted aryl amines and nitrogen heterocycles including pyrole, indole, imidazole, benzimidazole, and carbazole. The catalyst was characterized by EPR, UV, FT-IR, BET, AAS, TGA analysis, XPS, XRD, and HR-TEM.

Mane SN1, Et al. have proposed the work on Intensification of paracetamol (acetaminophen) synthesis from hydroquinone using ultrasound, this work deals with ultrasound assisted synthesis (UAS) of paracetamol from hydroquinone using ammonium acetate as an amidating agent. The optimization of various reaction and ultrasound parameters was performed to minimize the energy and time requirement. UAS of paracetamol was achieved at a lower temperature (60 °C) and the time (150 min) without formation of salt as a byproduct, making reaction green and inherently safer. On the other hand, the conventional process requires high reaction temperature (220 °C) and time (15 h). The quantification of the product was done by using high performance liquid chromatography (HPLC). Optimization of parameters revealed that the percent yield of 57.72% can be obtained in 150 min by performing the reaction in the ultrasound bath at 22 kHz frequency, 60 °C temperature, hydroquinone to ammonium acetate and

III. EXPERIMENTAL PROCEDURE

Figure 1 shows the experimental setup for the synthesis of Paracetamol. The reaction was performed in a 1L four-neck round bottom flask. Experimental set up was equipped with a thermocouple, a sampling port, agitator and motor, Dean-Stark condenser for acid reflux. The reaction temperature and agitator speed were continuously monitored.

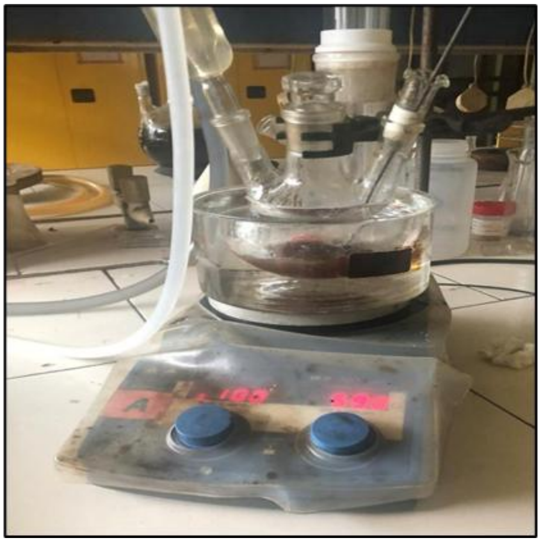


Fig. 1: Experimental setup for the synthesis of paracetamol

The reaction was carried out in a one liter four-neck glass round bottom flask (RBF). Initially, known weight of acetic acid was charged into the reactor & heated upto 60-80°C. P-aminophenol (PAP) was then added to the RBF at 60° C. The reactor mass was heated up to 90°C. A sample was withdrawn at 90°C and its weight was recorded at the zero time. Initially samples were taken at 20 min intervals for the first 3 h, thereafter the samples were withdrawn at 1hr interval upto 8th hour. The reaction was operated completely in a batch mode. After completion of reaction, the reaction mixture was transferred into a beaker and the same was placed in an ice bath for 1-2 h. The reaction crude consisted of the product, unreacted reactant and solvents.

The 10-20ml acetic acid solution was used to clean the reactor. Crude paracetamol crystals were formed at the bottom of the beaker and were separated by simply decanting the liquid layer. The acetic acid and water mixture was evaporated in a rotary evaporator to recover the dissolved paracetamol.

Activated charcoal treatment was preferred for decolourization of the crude paracetamol at 105°C, with total reflux for 1-2 h. Solids obtained from evaporation and the reaction mass (total crude paracetamol) were mixed together with sufficient quantity of water and activated charcoal (300 mesh size) in a three-neck RBF equipped with a temperature indicator, stirrer and condenser. This mixture was vacuum filtered in hot condition to separate charcoal. Further a hot water wash was given to the RBF to recover the paracetamol. The filtrate was cooled using an ice bath. The treatment is repeated as many times as needed for complete decolourization of paracetamol until white crystal solids are obtained. Water from crystallization was evaporated to collect dissolved paracetamol and treated for decolourization, if needed. The final product was dried and weighed.

Fig. 2 shows the actual color of PARA during the 1st, 2nd and 3rd treatment. It was observed that after 3rd treatment PARA product is white in color. The stability of PARA for extended period was also studied; it was observed that after 6 months, the PARA was white in color.

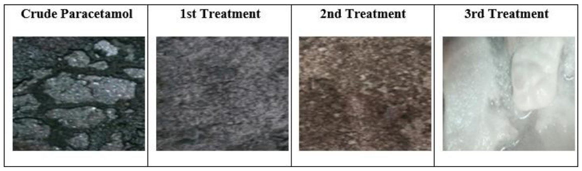
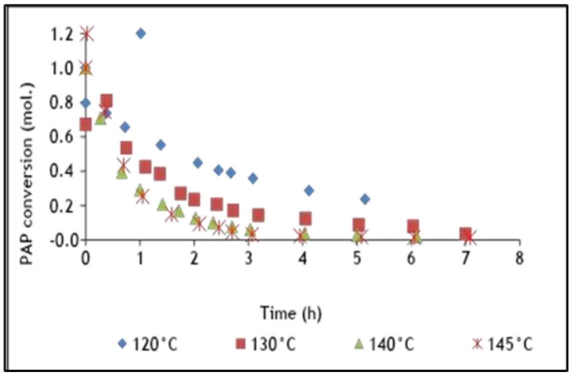


Fig. 2: Improvement in PARA colour after each treatment



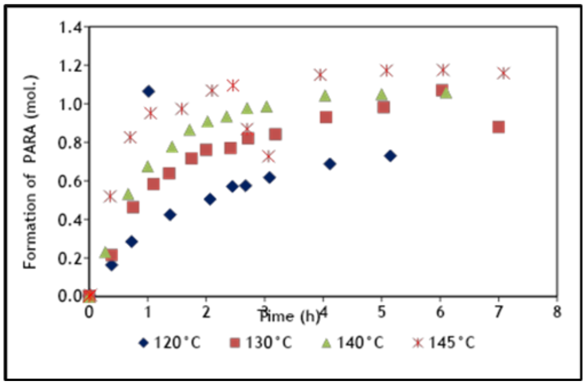


Fig. 3: Effect of temperature on p-aminophenol conversion and on paracetamol formation

IV. RESULT

Figure no. 3 represents the result of effect of temperature on p-aminophenol conversion as well as on paracetamol formation. Whereas figure no. 4 & 5 represents are effect of mole ratio & catalysts on p-aminophenol conversion as well as on paracetamol formation respectively.

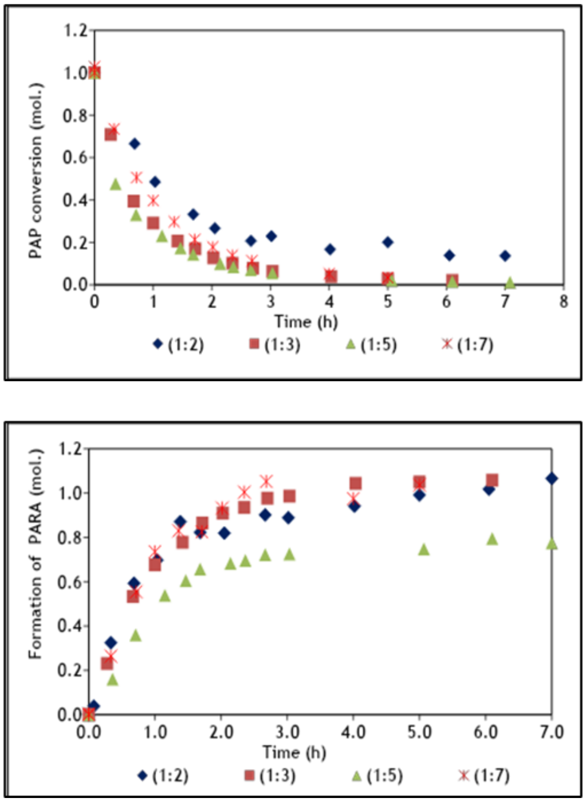


Fig. 4: Effect of mole ratio on p-aminophenol conversion and on paracetamol formation

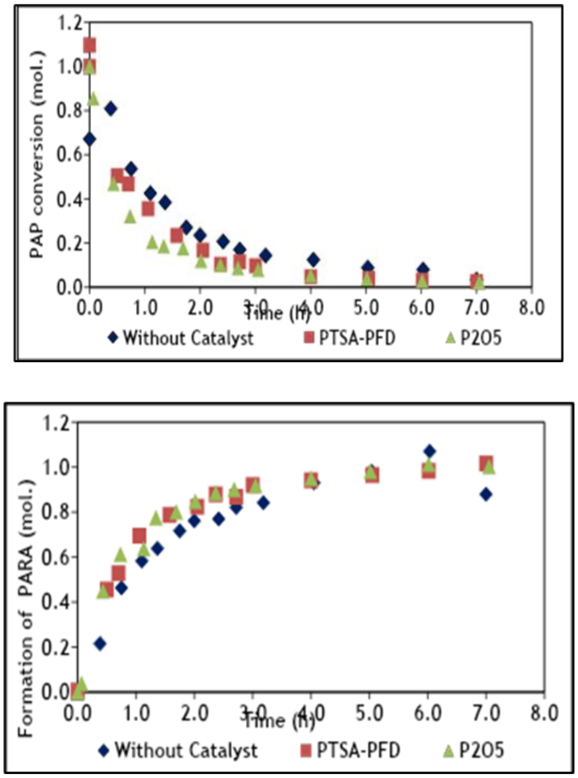


Fig. 5: Effect of catalysts on p-aminophenol conversion and on p-aminophenol conversion

V. CONCLUSION

The comprehensive study of the synthesis of Paracetamol (p-Acetamol) through the acetylation of p-aminophenol with acetic acid highlights the transformative power of process intensification in pharmaceutical manufacturing. The study focused on the meticulous selection of thermodynamic components and the development of a precise flow sheet. It was seen that specifying exact temperature and pressure parameters is important for maintaining stability and maximizing the rate of reaction. It was also observed that the reaction temperature plays a dual role, and it must be high enough to overcome the activation energy but regulated enough to prevent the degradation of p-aminophenol.

Furthermore, the optimization of the mole ratios of reactants ensured the complete conversion of the limiting reactant, which results increasing the overall efficiency of the plant. This specific catalytic combination demonstrated an exceptional ability to accelerate the acetylation process while ensuring high selectivity for p-Acetamol. By lowering the energy requirements and streamlining the reaction path, this study concludes that intensified catalytic systems are the key to making the production of this essential medicine more sustainable and economically viable on a global scale.

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