Intensification of paracetamol (acetaminophen) synthesis from hydroquinone using ultrasound

Swapnil N. Mane, Sagar M. Gadalkar, Virendra K. Rathod

PII: S1350-4177(18)30461-9
DOI: https://doi.org/10.1016/j.ultsonch.2018.07.029
Reference: ULTSON 4246

To appear in: *Ultrasonics Sonochemistry*

Received Date: 21 March 2018
Revised Date: 4 July 2018
Accepted Date: 20 July 2018

Please cite this article as: S.N. Mane, S.M. Gadalkar, V.K. Rathod, Intensification of paracetamol (acetaminophen) synthesis from hydroquinone using ultrasound, *Ultrasonics Sonochemistry* (2018), doi: https://doi.org/10.1016/j.ultsonch.2018.07.029

Intensification of paracetamol (acetaminophen) synthesis from hydroquinone using ultrasound

Swapnil N. Mane, Sagar M. Gadalkar, Virendra K. Rathod*

Department of Chemical Engineering,

Institute of Chemical Technology,

Matunga, Mumbai-400019,

India.

*Corresponding Authors: Email ID: vk.rathod@ictmumbai.edu.in, Phone: 91-22-33612020, Fax: 91-22-24145614

Abstract

Paracetamol (acetaminophen) is one of the most frequently used analgesic and antipyretic drugs. 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. While the conventional process requires high reaction temperature (220°C) and time (15h). The quantification of the product was done by using high performance liquid chromatography. Optimization of parameters revealed that the percent yield of 57.72% can be obtained in 150 minutes by performing the reaction in the ultrasound bath at 22 kHz frequency, 60°C temperature, hydroquinone to ammonium acetate and acetic acid in a molar ratio of 1:6:5, 125W power, 50% duty cycle and agitation speed of 300 RPM. Hence, ultrasound assisted synthesis can be considered as a process intensification tool for the synthesis of paracetamol and possibly other pharmaceutical compounds.

Keywords: Paracetamol; hydroquinone; process intensification; ultrasound; HPLC.

1 Introduction

N-acetyl-para-aminophenol (APAP), known as paracetamol or acetaminophen, belongs to N-arylamide class and is an important drug used for the treatment of pain and fever. Paracetamol is one of the utmost consumed drugs globally with a production of more than 100,000 tons per year [1]. Necessity of drug in this enormous amounts for pharmaceutical industry, substantiated with commercial aspects concerning the economic competence, lead to the requirement of manufacturing these compounds through substitute routes in order to attain high purity in short periods of time and with the consumption of a minimum quantity of solvents. To achieve best synthesis route, studies have been performed using different starting compound , such as p-nitro-chlorobenzene, nitrobenzene [2,3], *p*-nitrophenol [4] and hydroquinone [1,5]. Among these, hydroquinone method comprises direct acetylation without need of extra steps involved in other routes. In 2014, Joncour et al., established this green approach involving direct amidation of hydroquinone to obtain paracetamol with greater conversion [1] which eliminates the problems associated with the earlier techniques such as, the extra step involved, unwanted *ortho*-isomerization, generation of the sulfate salt etc. Although the route established by Joncour et al. has several advantages, it also unveils some glitches such as, time consuming (15 h) and requirement of high operating temperature (220°C). The use of ultrasound can be an intensification tool to overcome these issues, which can intensify the process with respect to lowering reaction time, temperature and possibly solvent requirement.

Nowadays, ultrasound is used successfully used as process intensification tool in the field of extraction bioactive compounds [6,7], synthesis of nanoparticles and pharmaceutical molecules [8,9]. Ultrasound enhances the chemical reactivity in a liquid medium through the generation and destruction of cavitation bubbles. The ultrasound wave propagates through the liquid medium in

subsequent compression and rarefaction cycles, when the rarefaction cycle dominates the attractive forces of the liquid or molecules present in it result in the formation of cavities. When these cavities collapse the energy for chemical and mechanical effect of ultrasound is produced leading to the generation of very high local temperatures and pressures [10]. Although ultrasound is used for synthesis of various organic products, it has not been tried for the synthesis of paracetamol to the best of knowledge. UAS is considerably faster, cleaner and eco-friendly comparable with classical organic synthesis. Thus, the study is focused to explore the application of ultrasound for the synthesis of paracetamol in a solvent-free reaction condition.

2 Materials and methods

2.1 Materials

Ammonium acetate AR grade, hydroquinone AR grade, glacial acetic acid, acetonitrile (HPLC grade), ethyl acetate AR grade and n-hexane AR grade were purchased from Thomas Baker (Chemicals) Pvt Ltd, and used without further purification.

2.1.1 Ultrasound assisted synthesis

Ultrasonic bath (model 6.5l, 200 H, dakshin, India) with the internal dimensions as 300 mm × 150 mm × 150 mm was used. Three neck flat bottom glass reactor of 50 mL capacity equipped with a mechanical stirrer was used for performing the reaction. The reactor was held in the bath at a sufficient water level based on maximum cavitation intensity to carry out the reaction. The position of the reactor in the ultrasonic bath was fixed according to the maximum efficiency of ultrasonic irradiation [11]. During the experiment, hydroquinone 2.2 g (0.02 mol), ammonium acetate 3.15 g (0.04 mol) and acetic acid 6.75 mL (0.1 mol) were added in a glass reactor. Then the reactor was placed in ultrasound bath with stirring and ultrasound irradiation. The reaction was carried out for 180 minute and samples were withdrawn at known time intervals to

determine the conversion. Various temperatures such as ultrasound power, molar ratio, duty cycle, temperature and agitation speed were optimized. In order to study the energy efficiency of the ultrasonic bath, calorimetric studies were performed. Amount of energy dissipated in the bulk of liquid was calculated by measuring the rise in temperature of a fixed quantity of reaction mixture in an ultrasonic bath for a given time. Power dissipation was calculated as per Sutkar et al. (2010) [12]. The analysis and quantitation of the product was done using HPLC analysis of crude reaction mixture.

2.2 Analytical method

2.2.1 High performance liquid chromatography (HPLC)

HPLC analysis of the crude reaction mixture was done using a JASCO (4000 series) system with a manual injector, pump (PU-4180) and UV/VIS (UV-4070) detector. JASCO Finepak SIL C18 column (250 x 4.6 mm, particle size 0.5 μm) was used as stationary phase with mobile phase comprising mixture of water and acetonitrile in the ratio of 70:30 (isocratic elution), at flow rate of 1 $mL.min^{-1}$ and detection wavelength of 254 nm. The percent yields were calculated from calibration curve obtained from different concentrations of standard paracetamol.

3 Results and discussion

3.1 Effect of temperature on conversion yield of paracetamol

Experiments were carried out to investigate the effect of temperature (Fig. 1) ranging from 30°C to 70°C by keeping other parameters constant including agitation speed of 300 rpm, molar ratio of hydroquinone to ammonium acetate and acetic acid 1:2:5 respectively, ultrasound frequency 22 kHz, power 50 W and duty cycle 50%. It was observed that 13.97%, 14.96%, 27.33% and 32.51% yield was obtained at 30°C, 40°C, 50°C and 60°C respectively. But further increase in

temperature to 70°C, leads to decrease in the yield. The rate of reaction increases with an increase in reaction temperature because vapor pressure of solvent and/or molecules plays an important role in cavitation effect that further affects the rate of reaction [13,14]. As higher temperatures favor nucleophilic substitution reaction, increase in yield was observed up to 60°C [1]. However, decrease in the yield can be related to decreased cavitation effect of ultrasound, as at higher temperatures the cavitation effect of ultrasound decreases. First, as the reaction temperature is increased, the vapor pressure of the system is also increased which leads to easier bubble formation (due to the decrease of the cavitation threshold), however, the cavitation bubbles formed contain more vapor. In general, the largest sono-chemical effects are seen at lower temperatures when a majority of the bubble contents is gas. In certain reaction systems, an optimum reaction temperature lead to more favorable results. In such systems, an increase in temperature causes increase in the kinetic of reaction up to a point at which the cushioning effect of the vapor in the bubble begins to dominate the system. When this occurs, the rate of the reaction decreases upon further increase in the reaction temperature [15]. The rate may also reach a plateau with temperature and then decrease as the temperature increases [16]. Therefore, considering the highest yield obtained, the temperature of 60°C was considered as optimum.

The reaction mechanism for conversion of hydroquinone (HQ) to acetyl para aminophenol (APAP) is illustrated in Fig. 2. The reaction of HQ with ammonium acetate was possibly progressed through the formation of para-aminophenol (PAP) as an intermediate, which further directly acetylated to APAP producing two water molecules as side product [1]. According to Joncour et al., at high temperature, ammonium acetate could be first dehydrated to acetamide and further reacted with HQ to form APAP, which indicated possible contribution of ultrasound as an

increase in localized temperature due to cavitation which was contributed in nucleophilic substitution reaction

3.2. Effect of irradiation power on conversion yield of paracetamol

In order to find out the optimum input power for this reaction, the experiments were carried out at irradiation power of 50W, 75W, 100W, 125W and 150W, keeping all other parameters constant, such as ultrasound frequency 22 kHz, temperature 60°C, agitation speed of 300 rpm, molar ratio of hydroquinone to ammonium acetate and acetic acid 1:2:5 respectively, and duty cycle 50%. Fig. 3 revealed that, a yield of 32.51% was obtained after 3 h with irradiation power of 50W and subsequent increase in power to 75W, 100W & 125W resulted in increased yield of 35.27%, 37.61% & 42.32% respectively. The irradiation power of 125W was considered as optimized power for proceeding experiments as further increase in power to 150 W did not show significant (43.45%) increase in the yield. It was found that as the amount of power delivered to the reaction mixture increases, the rate of the reaction increases to a maximum limit and then decreases with a continued increase in power [17]. A relatively small amount of energy supplied is often sufficient for the reaction to take place. If the energy is too low, the cavitation threshold may not be reached or the yield may be very low. Above the cavitation threshold the only effect of increase in power is to produce more bubbles, with each bubble having same cavitation energy level. A possible explanation for the observed decrease in rate at high powers is the formation of a dense cloud of cavitation bubbles which try to block the energy transmitted to the fluid. If a more number of cavitation bubbles are created in the bulk of the liquid, they are responsible for an absorption of the acoustic energy which lowers the effective yield of the reaction [13]. Calorimetric study has been carried out to evaluate the efficiency of ultrasonic bath. Different factors such as solvent, surface tension, viscosity and overall vessel geometry affect the power

dissipation. Dissipated power was computed from the temperature rise of the reaction mixture after specific time at 25 and 40 kHz frequency with varying irradiated power (50 to 150 W). Practical dissipated power was found to be 40.5, 47.8, 60.2 and 63.4 W for following input power of 50, 100, 125 and 150 W respectively. Increase in actual power dissipation from 125 to 150W was marginal i.e. 60.2 and 63.4 W respectively. Consequently, with an increase in power input to 150W was not contributed to yield improvement (43.45%), as compared to yield (42.32%) at power 125W. Therefore, further experiments were carried with optimized 125W power input.

3.3.Effect of molar ratio on conversion yield of paracetamol

Effect of different molar ratios of hydroquinone to ammonium acetate and acetic acid prove to be important in terms of reaction economics. In order to study the effect of molar ratio on ultrasound assisted reaction, a series of reactions were carried out by varying the molar ratio of hydroquinone to ammonium acetate and acetic acid. Firstly, experiments were focused on to optimize the concentration of ammonium acetate as it leads to incorporation of acetamido functionality. Thus, hydroquinone (HQ), ammonium acetate and acetic acid were taken in different ratios, keeping all other parameters constant (temperature 60°C, agitation speed of 300 rpm, ultrasound frequency 22 kHz, power 125W, and duty cycle 50%). The molar ratios of 1:2:5, 1:3:5, 1:4:5, 1:6:5, 1:8:5 and 1:10:5 gave percent yield of 42.32%, 43.12%, 43.19%, 57.72%, 57.24% and 51.28% respectively. Here, increasing the amount of ammonium acetate leads to increase in percent yield as ammonium acetate acts as nucleophile and is efficient amidating agent. Finally, the molar ratio of 1:6:5 was taken as optimum, as it can be seen in Fig. 4, that there is no significant increase in percent yield beyond this ratio.

As acetic acid is essential for acetylation and it also act as catalyst [1]. Acetic acid was taken in the ratios of 1:6:5, 1:6:6 and 1:6:8, which gave yield of 56.91%, 57.04% and 54.59% respectively, at constant parameters, temperature 60°C, agitation speed of 300 rpm, ultrasound frequency 22 kHz, power 125W, and duty cycle 50%. Consequently, the ratio of 1:6:5 was taken as optimum as there was no significant increase in the yield.

3.4. Effect of duty cycle on conversion yield of paracetamol

Duty cycle represents the actual exposure time of ultrasound irradiation to the reaction mass in one cycle, which can be varied by changing the on/off time of ultrasound [15]. On time indicates exposure of ultrasonic waves which leads to generation of cavitation and off time indicates resting period with no exposure of ultrasonic waves where cavitation bubbles gets sufficient time to enlarge and burst. Application duty cycle increases the time of cavitation action and ultimately the conversion. In order to investigate the effect of duty cycle on proceedings of reaction, reactions were performed at different duty cycles of 40%, 50%, 60%, 70% and 80%, keeping all other parameters like temperature 60°C, agitation speed of 300 rpm, ultrasound frequency 22 kHz, ultrasound power 125W, and molar ratio 1:6:5 as constant. Fig. 5 depicts that an increase in the duty cycle (on time) resulted into increase in corresponding percent yield. Therefore, duty cycle of 50% was taken as optimum considering economic and sustainability point of view. It is always recommended to operate the reaction at a lower duty cycle to reduce the possible damage to reaction mass by continuous exposure of ultrasonic waves. Also, keeping the ultrasound 'on' for a long time can damage the transducers, thus using recent instruments with better quality transducers should be preferred [18,19].

3.5. Effect of agitation speed on conversion yield of paracetamol

In order to investigate the effect of agitation speed on the reaction we carried out reactions at different speed in the range of 100 rpm to 400 rpm, keeping all other parameters constant like, temperature 60ºC, molar ratio 1:6:5 and ultrasound frequency 22 kHz, power 125W and duty cycle 50%. The results showed that the effect of agitation speed did not display significant effect on this reaction as the yields obtained at 100 rpm, 200 rpm, 300 rpm and 400 rpm gave the percent yield of 54.95%, 55.62%, 56.91% and 55.54% respectively. As this is a homogenous reaction, the mass transfer (physical effect) is not important. Another reason for this would be due to the overlapped effect of ultrasound over stirring, in which effective collision of molecules happens much more efficiently than that of stirring.

3.6 Comparison of conventional and ultrasound assisted synthesis of paracetamol

Ultrasound assisted synthesis was found that as the amount of power delivered to the reaction mixture increases, the rate of the reaction increases which claims, activation energy required for the nucleophilic substitution has been delivered through cavitation. The optimization of various reaction and ultrasound parameters was minimized the energy and time requirement of reaction. Fig. 6 shows the comparison of % yield of paracetamol using conventional and UAS. UAS of paracetamol was achieved at a lower temperature (60°C) and the time (150 min) without formation of salt as the byproduct, while the conventional process requires high reaction temperature (220ºC) and time (15h).

4. Conclusions:

Here, ultrasound was utilized successfully to intensify the yield of paracetamol by using hydroquinone, ammonium acetate and acetic acid as raw material. In the context of green technology, use of ultrasound resulted into safe operation with shorter reaction time. The

synthesis of paracetamol without salt production and water as the by-product gives the upper hand for its potential application. Optimization of parameters revealed that the percent yield of 57.72% can be obtained in 150 minutes by performing reaction in ultrasound bath. The use of ultrasound bath can be helpful for achieving the better yield of the product. The chemical effects due to cavitation phenomenon by ultrasound may be the reason for this reaction to proceed, as the physical effects are generally observed with the heterogeneous reactions. The reaction proceeds at relatively lower temperature than conventional method which is also additional advantage.

Reference

[1] R. Joncour, N. Duguet, E. Métay, A. Ferreira, M. Lemaire, Amidation of phenol derivatives: a direct synthesis of paracetamol (acetaminophen) from hydroquinone, Green Chem. 16 (2014) 2997.

[2] C. V Rode, M.J. Vaidya, R. V Chaudhari, Synthesis of p-aminophenol by Catalytic Hydrogenation of Nitrobenzene Abstract :, 3 (1999) 465–470.

[3] K. Min, J. Choi, Y. Chung, W. Ahn, R. Ryoo, P.K. Lim, p-Aminophenol synthesis in an organic / aqueous system using Pt supported on mesoporous carbons, 337 (2008) 97–104.

[4] Y. Du, H. Chen, R. Chen, N. Xu, Synthesis of p-aminophenol from p-nitrophenol over nano-sized nickel catalysts, 277 (2004) 259–264.

[5] A. Bhattacharya, V.C. Purohit, V. Suarez, R. Tichkule, G. Parmer, F. Rinaldi, One-step reductive amidation of nitro arenes:application in the synthesis of Acetaminophen, 47 (2006) 1861–1864.

[6] S.M. Gadalkar, V.K. Rathod, Pre-treatment of ferulic acid esterases immobilized on MNPs to enhance the extraction of ferulic acid from defatted rice bran in presence of

ultrasound, Biocatal. Agric. Biotechnol. 10 (2017) 342–351.

[7] A.S. More, S.M. Gadalkar, V.K. Rathod, Extraction of rapamycin (sirolimus) from Streptomyces rapamycinicus using ultrasound, Prep. Biochem. Biotechnol. 6068 (2017) 1–6.

[8] B.A. Bhanvase, S.H. Sonawane, Ultrasound assisted in situ emulsion polymerization for polymer nanocomposite: A review, Chem. Eng. Process. Process Intensif. 85 (2014) 86–107.

[9] H.A. Stefani, R. Cella, F.A. Dörr, C.M.P. De Pereira, F.P. Gomes, G. Zeni, Ultrasound-assisted synthesis of functionalized arylacetylenes, Tetrahedron Lett. 46 (2005) 2001–2003.

[10] J. Clark, D. Macquarrie, T.J. Mason, P. Cintas, Chapter 16 : Sonochemistry, (2002) 372–396.

[11] V.M. Kulkarni, V.K. Rathod, Mapping of an ultrasonic bath for ultrasound assisted extraction of mangiferin from Mangifera indica leaves, Ultrason. Sonochem. 21 (2014) 606–611.

[12] V. S. Sutkar, P. R. Gogate, Mapping of cavitational activity in high frequency sonochemical reactor. Chem. Engg. J. 158 (2010), 296-304.

[13] N. Pokhrel, P.K. Vabbina, N. Pala, Sonochemistry : Science and Engineering, Ultrason. Sonochem. (2015).

[14] G. V. Waghmare, M.D. Vetal, V.K. Rathod, Ultrasound assisted enzyme catalyzed synthesis of glycerol carbonate from glycerol and dimethyl carbonate, Ultrason. Sonochem. 22 (2015) 311–316.

[15] M. Ibisi, B. Brown, Variation of the Relative Intensity of Cavitation with Temperature, 41 (1967) 918–920.

[16] C.M. Sehgal, S.Y. Wang, Threshold intensities and kinetics of sonoreaction of thymine in aqueous solutions at low ultrasonic intensities, J. Am. Chem. Soc. 103 (1981) 6606–6611.

[17] M. Gutierrez, A. Henglein, Chemical action of pulsed ultrasound: observation of an unprecedented intensity effect, J. Phys. Chem. 94 (1990) 3625–3628.

[18] N.R. Khan, S. V. Jadhav, V.K. Rathod, Lipase catalysed synthesis of cetyl oleate using ultrasound: Optimisation and kinetic studies, Ultrason. Sonochem. 27 (2015) 522–529.

[19] H. Pan, Y. Zhou, O. Izadnegahdar, J. Cui, C.X. Deng, Study of sonoporation dynamics affected by ultrasound duty cycle, Ultrasound Med. Biol. 31 (2005) 849–856.

Figures caption

Fig. 1. Effect of temperature (℃) on conversion yield (%) of paracetamol at agitation speed of 300 rpm, molar ratio of hydroquinone to ammonium acetate and acetic acid 1:2:5 respectively, ultrasound frequency 22 KHz, power 50 W and duty cycle 50%)

Fig. 2. Proposed mechanism pathway

Fig. 3. Effect of irradiation power (W) on conversion yield (%) of paracetamol at ultrasound frequency 22 KHz, temperature 60℃, agitation speed of 300 rpm, molar ratio of hydroquinone to ammonium acetate and acetic acid 1:2:5 respectively, and duty cycle 50%)

Fig. 4. Effect of molar ratio on conversion yield (%) of paracetamol at temperature 60℃, agitation speed of 300 rpm, ultrasound frequency 22 KHz, power 125W, duty cycle 50%)

Fig. 5. Effect of duty cycle (%) on conversion yield (%) of paracetamol, at temperature 60℃, agitation speed of 300 rpm, ultrasound frequency 22 KHz, ultrasound power 125W, and molar ratio 1:6:5

Fig.6 Comparison of parameters for conventional and UAS of paracetamol

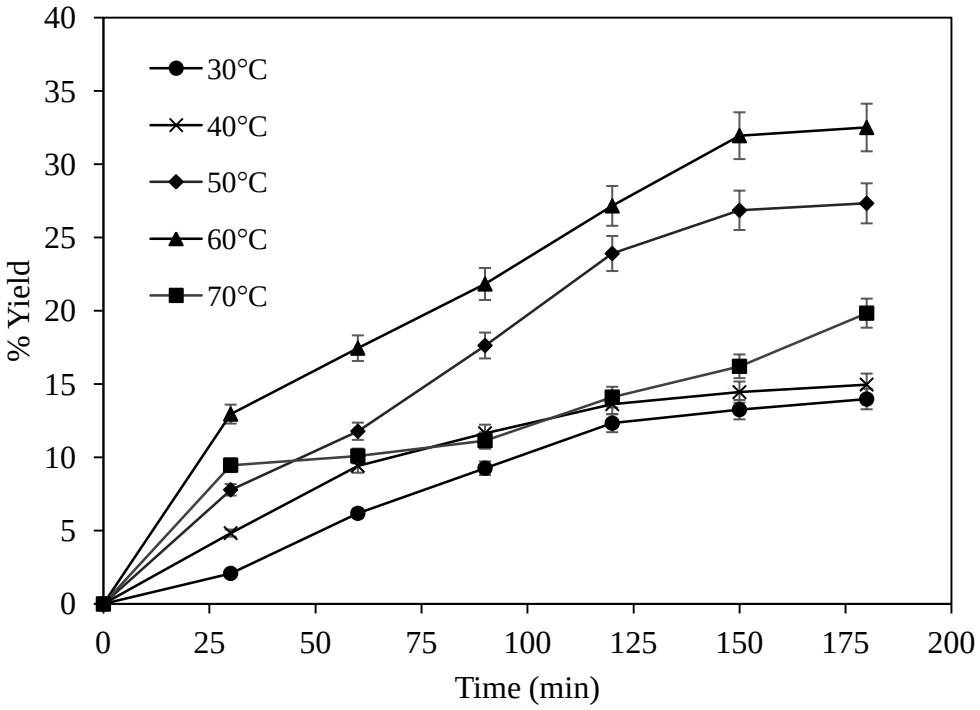


Fig. 1. Effect of temperature (℃) on conversion yield (%) of paracetamol at agitation speed of 300 rpm, molar ratio of hydroquinone to ammonium acetate and acetic acid 1:2:5 respectively, ultrasound frequency 22 KHz, power 50 W and duty cycle 50%)

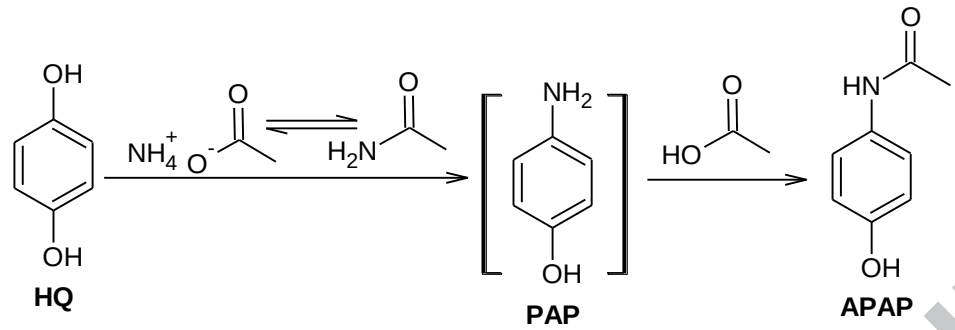


Fig. 2. Proposed mechanism pathway

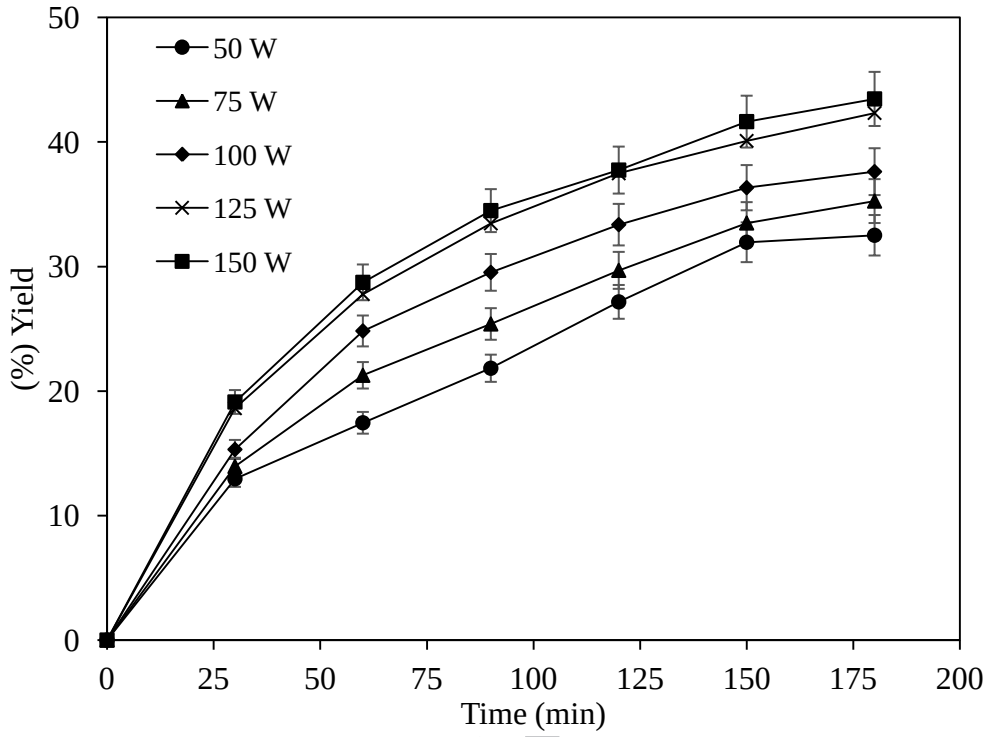


Fig. 3. Effect of irradiation power (W) on conversion yield (%) of paracetamol at ultrasound frequency 22 KHz, temperature 60℃, agitation speed of 300 rpm, molar ratio of hydroquinone to ammonium acetate and acetic acid 1:2:5 respectively, and duty cycle 50%)

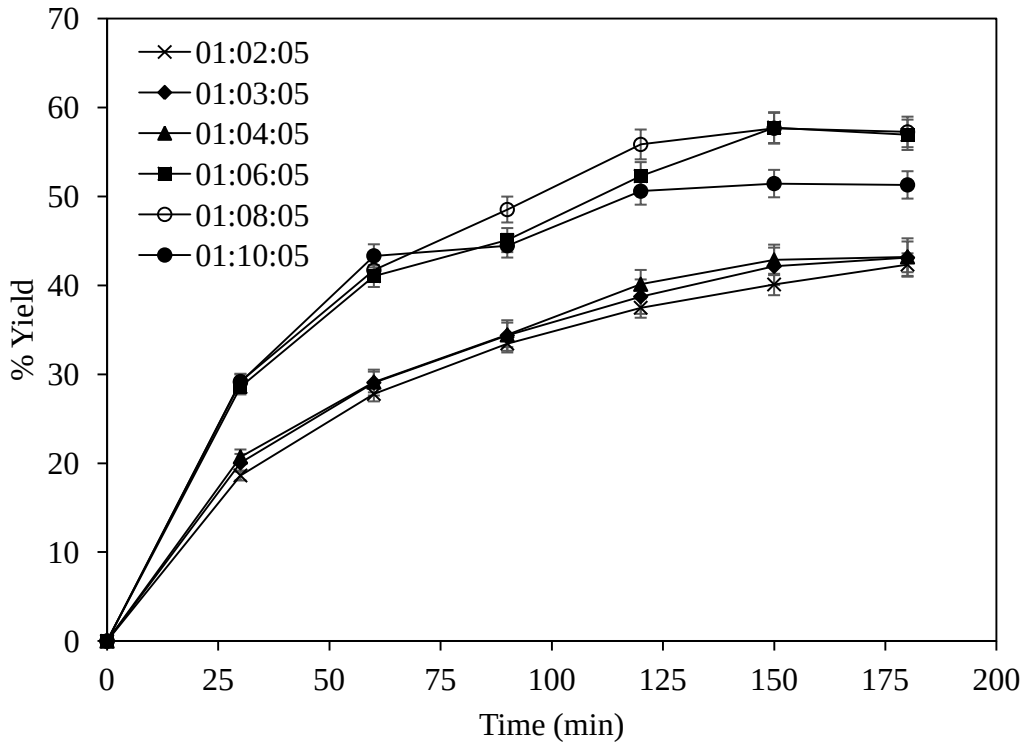


Fig. 4. Effect of molar ratio on conversion yield (%) of paracetamol at temperature 60°C, agitation speed of 300 rpm, ultrasound frequency 22 KHz, power 125W, duty cycle 50%)

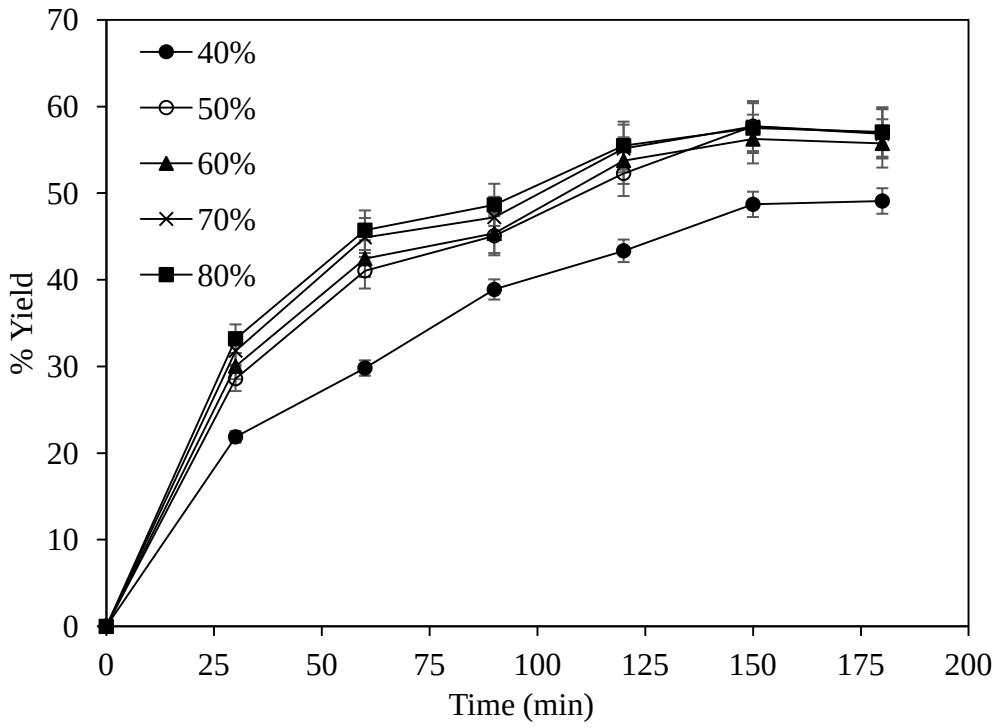


Fig. 5. Effect of duty cycle (%) on conversion yield (%) of paracetamol, at temperature 60°C, agitation speed of 300 rpm, ultrasound frequency 22 KHz, ultrasound power 125W, and molar ratio 1:6:5

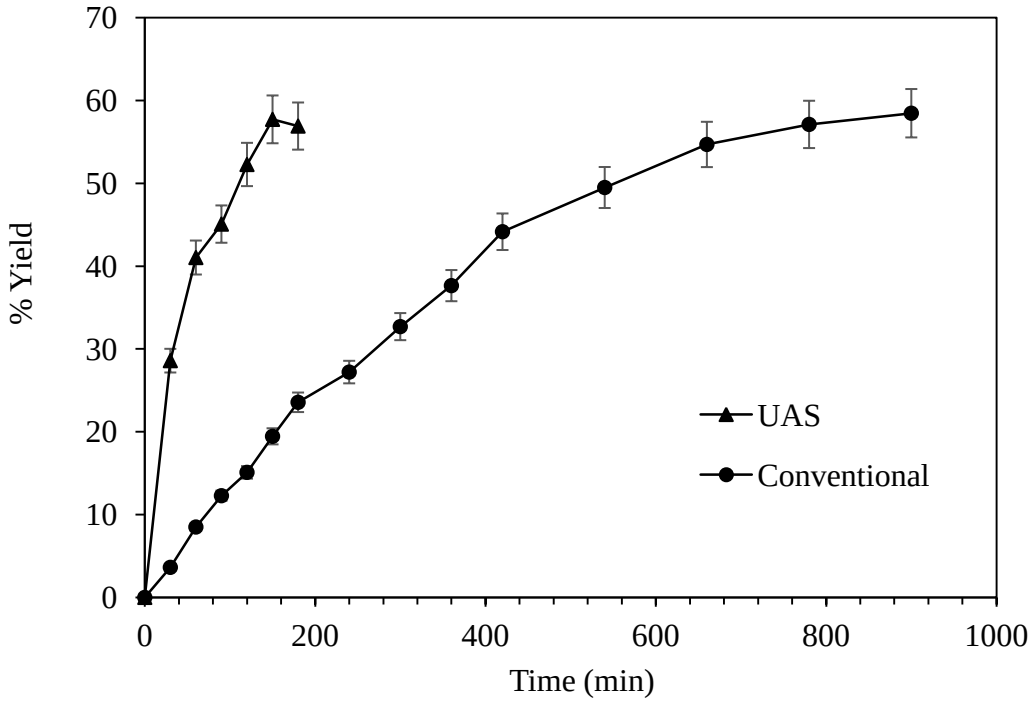
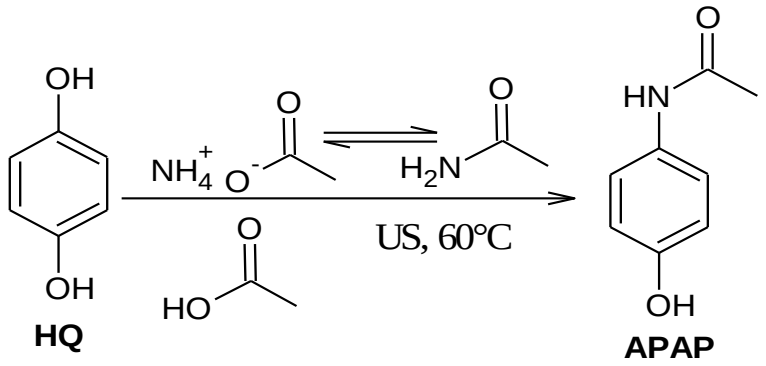


Fig.6 Comparison of parameters for conventional and UAS of paracetamol



Graphical abstract: Direct amidation of hydroquinone

Research Highlights

- Optimization of various reaction and ultrasound parameters was performed
- UAS of paracetamol was achieved without formation of salt as a byproduct, making reaction green and inherently safer
- Ultrasound assisted synthesis minimizes the energy and time requirement
- Cavitation can also be used to intensify the synthesis other pharmaceutical compounds