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AN EFFICIENT ONE-POT SYNTHESIS OF DIHYDROPYRIMIDINONES DERIVATIVES PROMOTED BY CHITOSAN BEADS

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Abstract: Chitosan-based microbeads as biocomposite was fabricated using simple drop-casting in the basic solution. These synthesized beads were used for the efficient synthesis of Dihydropyrimidine derivatives. The resultant composite was characterized by Fourier transform infrared spectroscopy, X-ray diffraction (XRD), scanning electron microscopy (SEM), Nuclear magnetic resonance spectroscopy (NMR), thermogravimetric analysis (TGA), and Dynamic scanning calorimetry (DSC). Then the performance of the metal-free catalyst for promoting by synthesis of dihydropyrimidinones derivatives was appraised. The model reactions were performed under conventional stirring and reflux conditions with the optimum amount of the catalyst and solvents. It was found that the composite was highly efficient and recyclable.

Keywords: Chitosan beads, biginelli reaction, metal-free catalyst, reusability, green synthesis

1. Introduction

Science and technology have recently focused on more environmentally friendly, sustainable resources and reused catalysts in an effort to reduce waste and the atom economy in the use of raw materials. [1-2] If we want to reduce the amount of garbage produced, every contribution—no matter how big or small—to the development of new "green" solutions is significant. [3-5] Consequently, biopolymers are desirable candidates for a biodegradable and non-toxic catalyst. A deacetylated version of the naturally occurring and renewable polymer "chitosan" is a promising candidate. It can be made quickly by treating inexpensive chitin with alkali. Chitosan has a special combination of environmentally friendly qualities, including the capacity to break down into harmless products, non-toxicity, biocompatibility, recyclable nature, physiological inertness, stability to air and moisture, and affordability. [6-8] By adding an aqueous alkali solution, filtering it, and reusing it without drying, it is possible to recover it quantitatively. It provides an exceptional yield for the desired good. Chitosan is a naturally occurring biopolymer derived from chitin, a substance found in the exoskeleton of crustaceans like shrimp, crabs, and lobster. It is a linear polysaccharide composed of randomly distributed beta-(1-4)-linked D-glucosamine and N-acetyl-D-glucosamine units. Chitosan has a variety of potential applications due to its unique properties, such as its ability to form a gel-like substance in acidic environments, its biocompatibility, and its ability to interact with other

molecules. [9-10] The physico-chemical properties of chitosan are governed by two crucial parameters: its DA and its molar mass. The presence of many hydroxy and amino groups endows chitosan with a high hydrophilicity and a high affinity not only for metals but also for peptides and fatty acids. Chitosan is a relatively easy-to-handle polymer with numerous shaping possibilities (flakes, beads, sponges, wires, films, membranes, etc.). [11-12] All of these physico-chemical features, combined with their valuable biological properties (nontoxic, biodegradable, and biocompatible), have led to an interest in chitosan in a large array of scientific fields. The promising achievements relating to chitosan as a supporter as an organocatalyst in its own right in heterogeneous catalytic reactions. [13] The few asymmetric reactions achievements being very recent, we also cover approaches providing achiral products to give the reader an overview of this steadily growing field of research. [14]

The Biginelli reaction is a multi-component reaction that is used to synthesize 3,4-dihydropyrimidin-2(1H)-ones (DHPMs). [15-16] The Biginelli reaction involves the reaction of an aldehyde, a β-ketoester or β-diketone, and urea or thiourea in the presence of a catalyst, typically a Lewis acid such as zinc chloride or titanium tetrachloride. The reaction proceeds via a condensation reaction between the aldehyde and β-ketoester or β-diketone to form an enamine intermediate. The urea or thiourea then reacts with the enamine to form the DHPM product. The Biginelli reaction has several advantages, including its simplicity, high yield, and readily available starting materials. [17] The reaction can be carried out under mild reaction conditions, making it a useful tool for the synthesis of a variety of DHPM derivatives. In addition, the reaction can be easily scaled up for industrial applications. The DHPM products synthesized via the Biginelli reaction have a variety of biological activities, including anti-tumor, anti-inflammatory, and anti-microbial properties. [18] As a result, the Biginelli reaction has become an important tool for discovering and developing new pharmaceuticals. The original method offered several limitations, such as low yield of products in the case of substituted and aliphatic aldehydes, harsh reaction conditions, and long reaction time. Due to their important biological activities, several improved protocols have been reported. In the classical Biginelli conditions, low yields and difficult isolation of the products are the main drawbacks because of the strongly acidic conditions, particularly when substituted aromatic or aliphatic aldehydes and thiourea were employed. [19-20] Chitosan-supported Biginelli reaction is a modified version of the Biginelli reaction that involves the use of chitosan as a support material for the catalyst. [21] The chitosan-supported catalyst is then used to facilitate the reaction between the aldehyde, β-ketoester or β-diketone, and urea or thiourea to produce the DHPM product. The use of chitosan as a support material for the catalyst offers several advantages, such as being biodegradable and non-toxic, making it an environmentally friendly alternative to traditional support materials. Additionally, chitosan has a large surface area and high porosity, which provides a large number of active sites for catalysis and allows for efficient reaction kinetics. The chitosan-supported Biginelli reaction has been shown to be an effective method for synthesizing DHPMs, with high yields and selectivity. [22] This method has been applied to the synthesis of a variety of DHPM derivatives with potential pharmaceutical applications, such as anti-inflammatory, anti-tumor, and antimicrobial activities. Furthermore, the chitosan-supported catalyst can be easily recovered and reused, making the reaction more sustainable and cost-effective.

2. Materials and Methods

Chitosan (Mw-130KDa deacetylation degree 78%), benzaldehyde, urea, ethyl acetoacetate, acetic acid, K2CO3, NaOH, MeOH, and EtOH were used for the synthesis of the catalyst and the analysis of its catalytic activity. The Sigma-Aldrich Chemical Company was utilized to obtain all of the aforementioned chemicals and reagents, which were then employed without additional purification.

3. Experimental section

3.1. Preparation of Catalyst: Synthesis of chitosan beads

Chitosan beads were synthesized according to the literature. [23] Briefly, chitosan (2 g) was dissolved in an acetic acid solution (100 mL, 2%) and kept under stirring for three h to obtain a homogeneous solution. Afterward, the chitosan solution was transferred to a burette and gradually dropped into NaOH aqueous solution (0.5 M) to form small chitosan beads, as shown in **Fig. 1.** The beads were kept overnight in the basic solution and subsequently rinsed with distilled water.
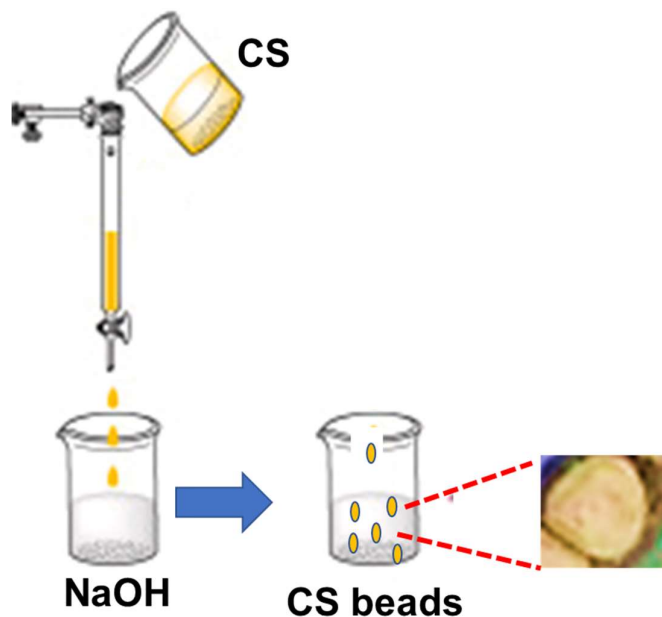

Figure 1: Fabrication of Chitosan beads.

3.2. Synthesis of DHPMs derivatives using Chitosan

Aldehydes (1 mmol), ethyl acetoacetate (1 mmol), urea (1.5 mmol), and beads (30 mg) were all combined in 10 mL of water and then sonicated for 15 minutes, as shown in scheme x. Thin-layer chromatography was used to continuously track the reaction's development. Beads were dried at 60 °C after the reaction was finished and then rinsed with distilled water before being used for the next reaction cycle. Following the solvent's evaporation, column chromatography recovered and purified the organic product.

4. Result and Discussion

4.1. Characterisation of Chitosan beads

The synthesized beads were characterized in detail. The FTIR spectrum shows the bands at roughly 1645 cm-1 (C=O stretching of amide I) and 1325 cm-1 (C-N stretching of amide III), respectively, provided evidence of the presence of residual N-acetyl groups, **Fig. 2a**. The tiny band at 1550 cm-1 that corresponds to for amide II's which suggests N-H bending was not present. This third band distinguishes conventional N-acetyl groups, and other bands most likely overlapped it. The main amine's N-H bending may be seen as a band at 1589 cm -1. The existence of bands at about 1423 and 1375 cm-1 confirmed the CH2 bending and CH3 symmetrical deformations. The C-O-C bridge's asymmetric stretching is responsible for the absorption band at 1153 cm-1. C-O stretching shows bands at 1066 and 1028 cm-1 are present. XRD pattern of pure Cs film showed lower intensity broad peaks at 2$\theta \approx$ 8.2, 11.4, 18.2, and 23o, which corresponds to d-spacing of 20.8, 7.5, 4.9, and 3.9 Å, respectively, as shown in **Fig. 2b**. The former two peaks are associated with the crystalline form II of CS due to H-bonded network with appreciable deacetylation degree.
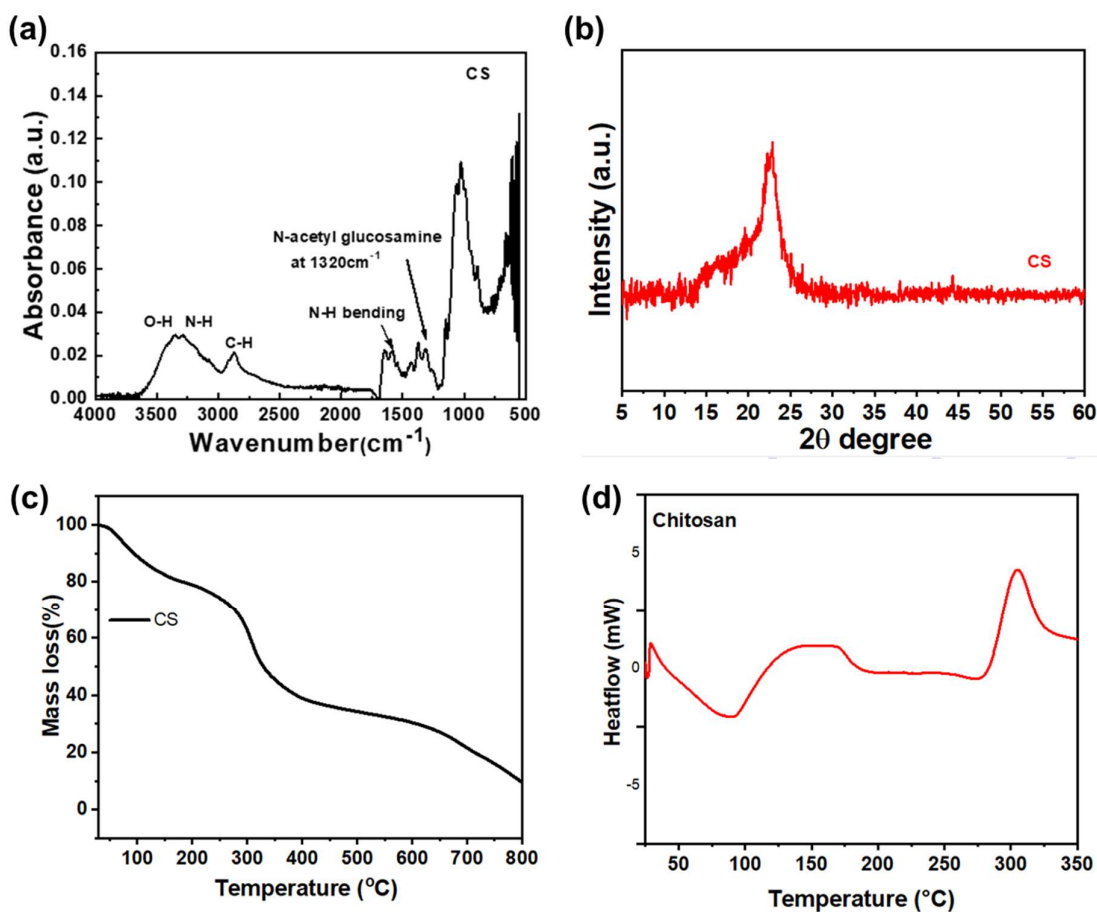

Figure 2: Charcaterisation of Chitosan beads: (a) FTIR spectrum; (b) Powder XRD; (c) TGA and (d) DSC analysis of Chitosan beads.

CS showed an endothermic transition at 80^{0}C due to the loss of water with a Tg of 178^{0}C, as shown in **Fig. 2c**. Due to the presence of hydrophilic features in chitosan, the first mass loss of 150 ^{o}C is attributed to the loss of water adsorbed in films, which is consistent with the DSC results, **Fig. 2d**. Chain degradation of chitosan is attributed to the mass loss at about 300^{0}C.
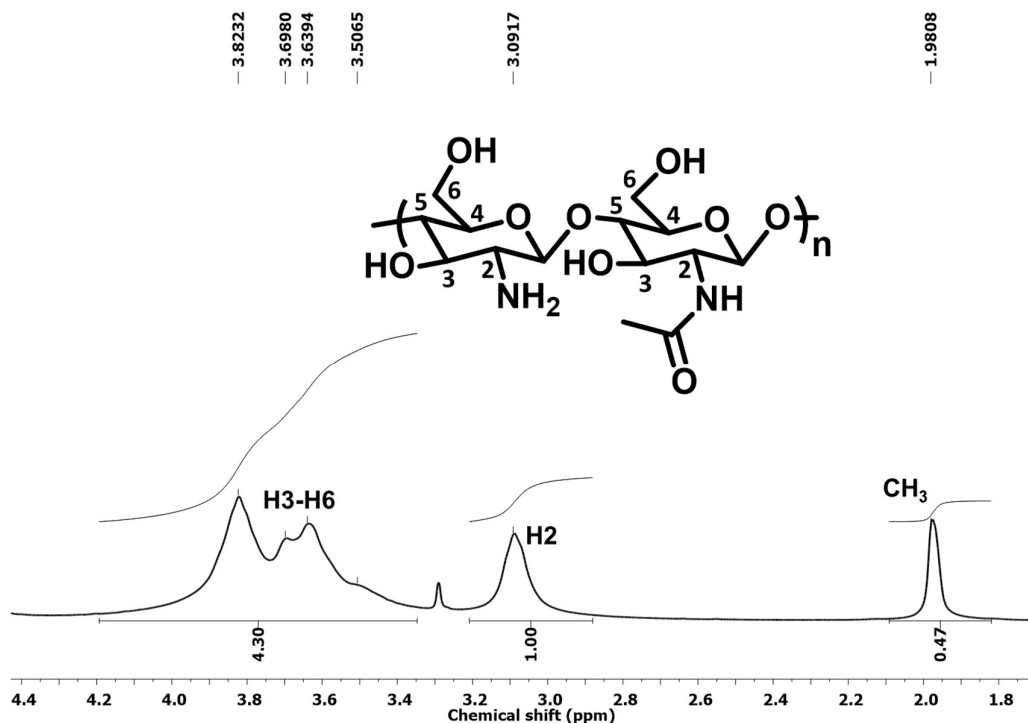
Figure 3: Charcaterisation of Chitosan beads: ^{1}H NMR spectrum of Chitosan beads.

The ^{1}H NMR profile of chitosan was received from Sigma Aldrich as such. We can get a fingerprint spectrum of each molecule using this method. There were recognized chitosan characteristic peaks in our sample. The signals of the aldohexoses' H2, H3, H4, H5, and H6 overlap in the range between 3.8 and 4.2 ppm, **Fig. 3** making evaluation challenging. A peak was identified as glucosamine anomeric H (H-1), and the signal at five ppm was identified as anomeric H1-N acetyl glucosamine (H-1). This is because the signals of the anomeric protons (H1) are visible at 5.25 ppm. The peak at 2.5 ppm was determined to be the hydrogens of the methyl group of N-acetyl-glucosamine, and the peak at 3.5 ppm was identified as H2 glucosamine. The peak represented the solvent's H at 4.75 ppm. The degree of deacetylation (DD) of chitosan can also be determined by 1H NMR, a reliable approach commonly used in the literature to make this determination. The integral of a few peaks in the chitosan's 1H NMR spectra was utilized to calculate the DD. For this computation, there are various formulae. The average DD in our example was 76.47% 4.08%, consistent with the range suggested by the supplier (75%).

4.2. Preparation and Morphology Evaluation of the Chitosan beads

The visual and the zoom-out image of the chitosan beads has shown in **Fig.4a and b**. To look into their surface architecture, FE-SEM was used to characterize the as-prepared spongy beads, as illustrated in **Fig.4c**. The cross-sectional view of a chitosan bead is depicted in Figure **Fig.4d**, which clearly demonstrates its extremely fibrous character and porous structure. It is crucial to understand that drying significantly affects the chitosan microbeads' shape. The as-prepared wet beads were dried in two distinct ways to examine the effects of drying: The beads were immediately frozen at 80 °C and subsequently dried in the presence

of vacuum in I a straightforward air drying process and (ii) a freeze-drying process. The air-dried beads show their stiff, impermeable structure. On the other hand, high porosity, freeze-dried chitosan beads were discovered to have an aerogel-like structure. According to the literature, freeze drying reduces the gel's shrinking force, which enhances porosity.
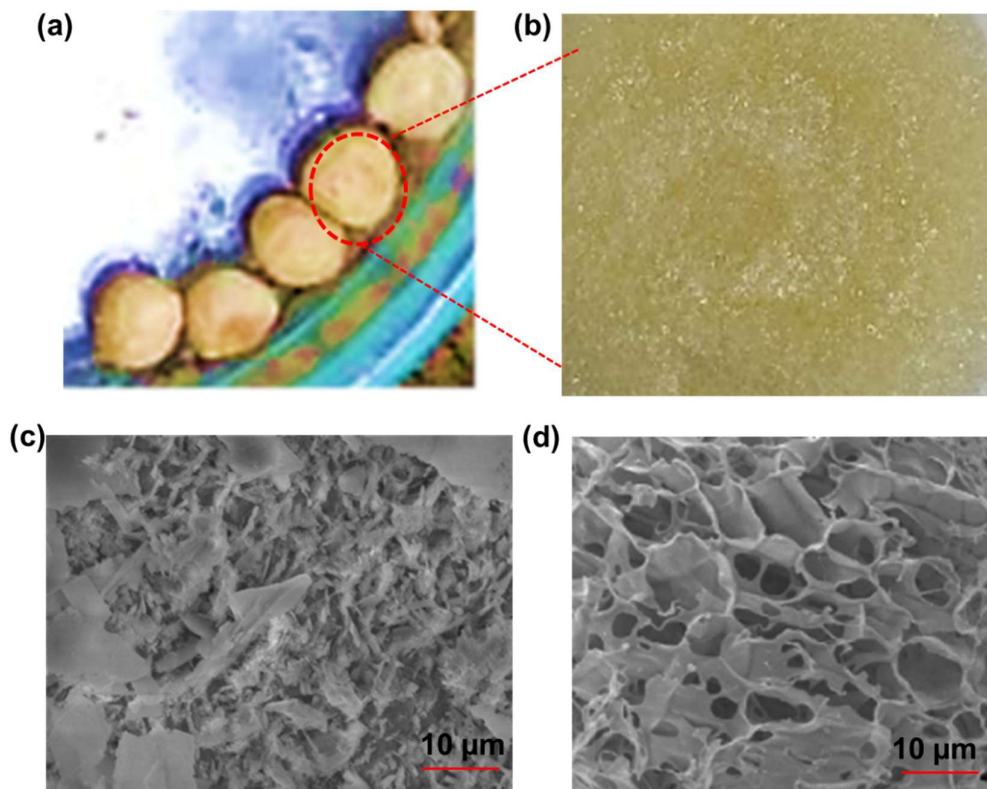

Figure 4: Charcaterisation of Chitosan beads: (a) Optical images; (b) Zoom out optical image; (c) Surface SEM image and (d) cross sectional image of Chitosan beads.

4.3. Catalyst activity

In this research, the aim was to develop an environmentally benign protocol for chemical synthesis. The model reactions were performed under conventional stirring and reflux conditions with the optimum amount of the catalyst and solvents, **Fig. 4**. The results implied that the reaction times were near about 70 min in both reflux and stirring conditions. A librray of different DHMPs derivatives with their respective yield mentioned in the **Table 1.**
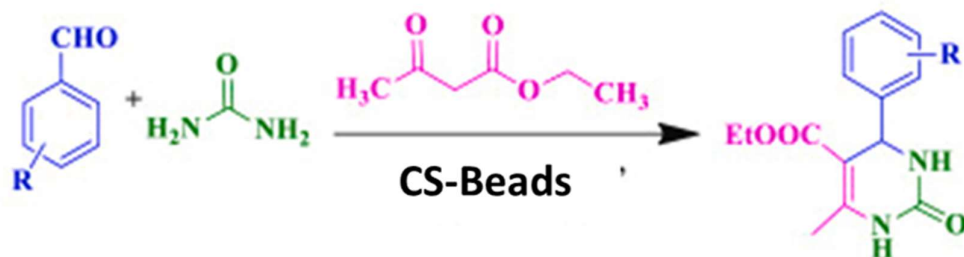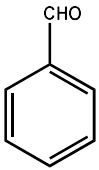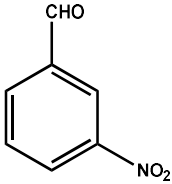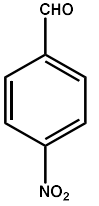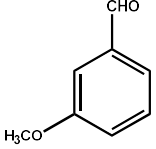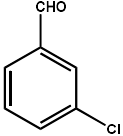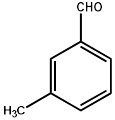

Figure 4: Synthetic scheme of Biginelli reaction using chitosan beads as a catalyst.

Table 1: Library of different derivative of DHPMs product.

S. No.	Substrate	Product Yield (%)
1	CHO (benzaldehyde)	80
2	CHO, NO$_2$ (3-nitrobenzaldehyde)	85
3	CHO, NO$_2$ (4-nitrobenzaldehyde)	87
4	CHO, H$_3$CO (3-methoxybenzaldehyde)	89
5	CHO, Cl (3-chlorobenzaldehyde)	78
6	CHO, H$_3$C (3-methylbenzaldehyde)	76

4.4. Effect of different M.W of chitosan on product yield

Three different types of chitosan were employed in the study to determine the proper molecular weight for the chitosan catalyst, and it was found that chitosan with a high molecular weight provides the highest yield of the desired product, as seen in **Table 2**. Chitosan's molecular weight decreases cause the yield to drop.

Table 2: Effect of M.W. of CS on product yield.

Type of CS	Time (min.)	Temp. (◦C)	Yield (%)	Recovery of Catalyst (%)
High M.W.	60	60	85	78
Mid M.W.	72	60	87	85
Low M.W.	88	60	78	83

4.5. Effect of reaction time

The reaction was observed at various periods for the model reaction in the presence of chitosan beads in 2% aqueous acetic acid solution at 60 °C. In order to examine the impact of reaction duration from 5 min. to 80 min. on the yield of the product. From 60-90 min., a noticeable increase in yield was seen. The product's yield peaked after 90 min., and even when a longer response time was used, no further improvement was seen. As a result, 90 min. was determined to be the ideal reaction time.

4.6. Reusability Studies and Analysis of Reused beads

An essential criterion for evaluating the adoption of a heterogeneous catalyst for commercial applications is its repeatability with high product yield. In the production of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one, the reusability of the beads was examined. It was discovered that the catalyst was successfully reusable up to 4 repeated cycles with a retention of more than 80% of its initial activity. FTIR spectral patterns of the catalyst beads were collected to evaluate the stability and makeup of the recycled catalyst. **Figure x** shows that the catalyst was reused and still maintained all of the fresh bead's unique bands, demonstrating the resilience of the beads even after numerous passes.
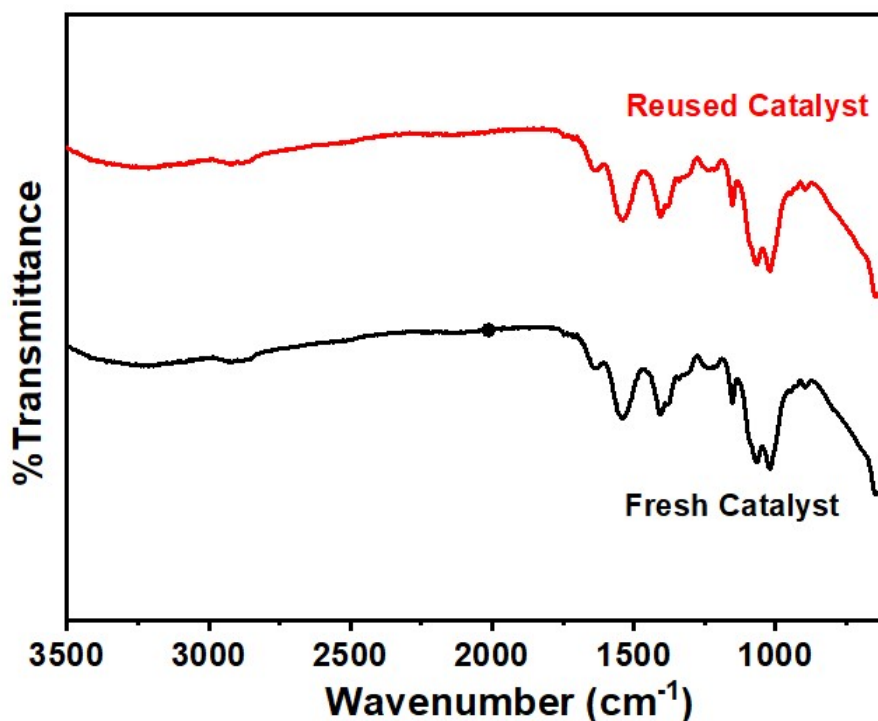

Figure 5: FTIR spectrum of fresh and reused beads (Resusability of catalyst)

4.7. Comparative studies

We compared the performance of the catalyst for synthesizing the model dihydropyrimidinone with the performance of various previous catalysts. Several techniques utilizing various catalysts have been documented, as shown in **Table 3**. Chitosan beads based catalyst has the advantages of easy recovery and recyclability compared to homogeneous catalysts. The advantage of bead-CDNS over polymeric catalysts is that it is more

biocompatible. This comparison study concludes that bead-CDNS is a powerful catalyst that may accelerate the model reaction under mild reaction conditions and that its activity is comparable to that of already reported catalysts.

Table 3. Comparative study of different catalysts.

S.No.	Catalyst	Time (Min.)	Yield (%)
1.	No Catalyst	50	60
2.	Sulfamic acid	30	72
3.	$P_2O_5.SiO_2$	16	70
4.	Current Work	60	85

5. Conclusion

In summary, chitosan beads were created using a simple drop process in basic media. After that, the resulting composite was examined and used as a metal-free catalyst to speed up the Biginelli reaction to produce dihydropyrimidinone derivatives in aqueous environments. The catalyst's ability to catalyze both reactions efficiently to produce the required products in high yields in a brief reaction time was discovered through research on the catalytic performance of the catalyst. The catalyst that was created had an activity that was better than or on par with some of the catalysts that had been previously described. The catalyst could also be easily taken out of the reaction mixture and used again for five runs. The ability of CS beads to act as a molecular shuttle is thought to play a part in catalysis. The current approach is an environmentally friendly technology because it uses biocompatible carbohydrates, conducts the reactions in aqueous media, highly recyclable catalysts, and uses ultrasonic irradiation.

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