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Enhancing the Effectiveness of Paracetamol Tablets with Chitosan Nanoparticle

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Abstract: Recently chitosan nanoparticles have received great interest for pharmacological toxicity and nanomedicine as a drug release system with improved bioavailability. This study aimed to prepare chitosan nanoparticles and explore the application of chitosan nanoparticles in pharmaceutical formulations, specifically in improving the formulation of paracetamol tablets for medical application. Chemical method was used for the preparation of the nanoparticles, Field Emission Scanning Electron Microscopy (FE-SEM), Atomic Force Microscope (AFM), X-Ray Diffraction (XRD) and Fourier Transform Infrared spectroscopy (FT-IR) techniques used to evaluate the morphology, topography and chemical structure of the precipitated nanoparticles. The revealed Nano-sphere like structures with dimeters of 41 to 74 nm. Chitosan nanoparticles have good binding, disintegrating and biodegradable properties, therefore it was used to improve the prepared paracetamol tablets. In this study, the tablets were prepared using a conventional wet granulation process. The results showed a good flowability property and an excellent compressibility profile compered to PVP K30. The physical properties of the prepared tablets were evaluated and the results showed an improvement in hardness and friability tests in prepared tablets compared to commercial tablets. The *in-vitro* drug release profiles for prepared and commercial tablets were evaluated in three distinct dissolution media (pH 0.1 HCl, pH 4.5 acetate buffer and pH 5.8 phosphate buffer). The results demonstrated nearly complete release of the prepared drug, with 100% released at approximately 20, 18, and 16 minutes, respectively. Based on the results, we can conclude that the chemical method was successful in preparing chitosan nanoparticles. In addition to that, it may be concluded that it is possible to improve the commercial paracetamol tablets using chitosan nanoparticles as a binder instead to PVP K30. Paracetamol tablets that contains chitosan nanoparticles have been successfully proved in enhancing of physical and chemical properties.

Keywords: Chitosan, Nanoparticles, Paracetamol, Tablet binder, Formulation.

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Introduction

Paracetamol, which is a recommended international name for acetaminophen (acetyl-p-aminophenol, APAP), was synthesized by Morse in 1878 and first utilized in medicine by Von Mering as an antipyretic/analgesic in 1893 (1). Today, Paracetamol remains a widely used over- the-counter (OTC) drug and ranks among the world's top-selling analgesics (2, 3). Researchers are becoming increasingly interested in chitosan and its nanoparticles because to its improved structural and functional qualities (4). Historically, chitosan was first described by Rouget in 1859, and formally named by Hoppe-Seyler in 1894 (5). Commercial chitosan was mainly produced from the chemical

deacetylation of chitin from marine organisms (6). Chitosan is a cationic polysaccharide and effectively accessible, biodegradable, biocompatible, nontoxic, and has pharmacological properties. In this manner, chitosan expanding happened in biomedical and pharmaceutical applications because of its diverse properties including antifungal (7), wound healing (8), antimicrobial (9), antioxidant (10), mucoadhesive (11), antitumor (12), anti-inflammatory (13), and antihyperglycemic (14) activities.

Chitosan hydrochloride has recently gained acceptance from regulatory authorities, as it has been included in the 4th edition of the European Pharmacopoeia (15). Efforts are ongoing to explore new ways of utilizing chitin and chitosan in co-processing techniques to create a product with potential as a direct compression excipient. (16). Chitosan has garnered significant attention as a potential pharmaceutical excipient in recent decades. It has been thoroughly evaluated for various conventional excipient applications, including its use as a binder in wet granulation for drug tablet preparation (17).

Chitosan has emerged as a preferred material for nanoparticle formation over the past decade, leveraging its inherent properties to enhance nanoparticle characteristics. Nanoparticles are distinguished by their small size and high surface-to-volume ratio, making them inherently mucoadhesive. This property enhances their ability to provide prolonged protection, stability, and extended release in the body, making them suitable for a wide range of medications (18). Various methods have been utilized for the synthesis of chitosan nanoparticles. Currently, five primary techniques are recognized: ionotropic gelation, microemulsion, emulsification-solvent diffusion, polyelectrolyte complexation, and the reverse micellar method (19).

The study aims to explore the application of chitosan nanoparticles in pharmaceutical formulations, specifically in improving the formulation of paracetamol tablets.

Materials and Methods

Chemicals used

Chitosan (Titan biotech LTD, India), Glacial acetic acid (Chem-Lab NV, Belgium), Hydrochloric acid(Sigma-Aldrch, India), Glutaraldehyde(LOBA Chemie laboratory reagents, India), n.Hexan (Chem-Lab NV, Belgium), Disodium hydrogen phosphate and sodium dihydrogen phosphate(LOBA Chemie laboratory reagents, India), Tween80 (polysorbate)(Viswaat Chemicals LTD. India), Paracetamol (Hebei Jiheng pharmaceutical Co. Ltd., China), Maize starch (Roquette Freres, France), Colloidal silicon dioxide (Pearl industries limited, UK), Magnesium stearate (Pearl industries limited, UK), Sodium starch glycolate (Pearl industries limited, UK), Acetonitrile(LOBA Chemie laboratory reagents, India), pH 1.2 HCI (prepared by dilute 8.34 ml of 37% concentrated HCl to 1000 ml by deionized water), pH 4.5 Acetate buffer (prepared by dissolving 2.99 gm of sodium acetate with 1000 ml of deionized water then the pH adjusted to 4.5 with 2N acetic acid), pH 5.8 phosphate buffer (prepared by dissolving 12.93 gm of Sodium dihydrogen phosphate and 1.69 gm of disodium hydrogen phosphate to 1000 ml deionized water and the pH adjusted to 5.8 by 0.2M Sodium hydroxide).

Devices used

Field Emission Scanning Electron Microscopy (FESEM) (TESCAN, Czech Republic), Fourier Transform Infrared spectroscopy (FT-IR) (Thermo

iS5, UK), X-Ray Diffraction (XRD) (Phillips PW 1830,USA), Atomic Force Microscope (AFM), (Park Systems Model XE-100, Korea), Magnetic Stirrer (MSION scientific Co. LTD, China), Centrifuge (REMI Co. Limited, India), Rapid mixer granulator (AIRPAC, India), Fluidized bed drier (AIRPAC, India), Double cone mixer (AIRPAC, India), Tablet compression machine (AIRPAC, India), Hardness tester (Mecmesin BFG 500N, UK), Friability tester (ElectroLab. EF-1W, India), Disintegration tester (Electrolab TDT -05 D, India), HPLC (Shimadzu LC- 2040C, Japan), Dissolution tester (ElectroLab. TDT-06 T, India).

Preparation of chitosan nanoparticles

Chitosan nanoparticles were prepared using chemical method. The chemical method is preferred for its simplicity and cost-effectiveness. As shown in Figure 1. Two solutions were prepared, 1st solution (A) organic solution and the 2nd solution (B) aqueous. The organic solution was prepared by dissolving 5 ml of the stabilizer tween 80 (poly sorbate 80) and 5ml of glutaraldehyde in 500 ml of n-Hexane with continuous mixing for 30 min. At the same time, the aqueous solution was prepared by dissolving 5ml of glacial acetic acid and 2.5 gm of chitosan in 500 ml of deionized water with continuous mixing for 30 min. Solution A was loaded into solution B dropwise under continuous stirring. Nanoparticles were created with a surfactant, and the system was stirred overnight at room temperature to ensure the completion of the cross-linking process. The organic solvent was evaporated under low pressure using a high pressure vacuum, then the nanoparticles were centrifuged by 14,000 RPM centrifuge, and the precipitated materials was dried in 45 ^{o}C oven (20-22). Then the chitosan nanoparticles finally were produced.

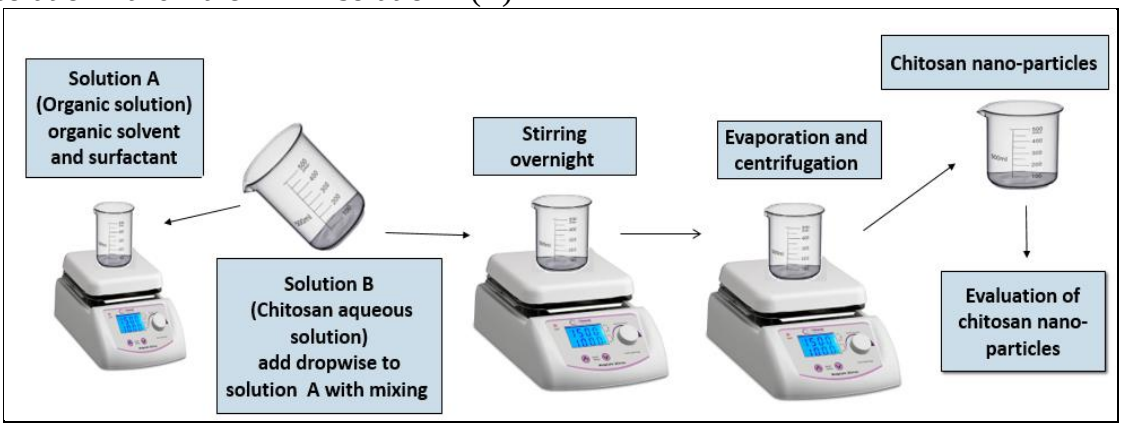

Figure (1): Chitosan nanoparticles preparation steps

Preparation of paracetamol chitosan nanoparticles tablets

Paracetamol is used in this study as a model drug to evaluate the effectiveness of chitosan nanoparticle in tablet formulation. Paracetamol chitosan nanoparticles tablets were formulated as shown in Table 1, each tablet of 640 mg containing 500 mg of paracetamol as the API (Active Pharmaceutical Ingredient). A conventional wet granulation process was used to produce paracetamol tablets. Paracetamol was mixed with maize starch and chitosan in a small-scale Rapid Mixer Granulator (RMG) until the powder was well mixed, then granulated in RMG with low speed for 15min with a slurry of chitosan in water (binder solution) prepared in a stainless steel container.

The resulting granules were dried at 35 °C using a Fluidized Bed Drier (FBD) until moisture content was 2.5 percent. With a 1000 µm sieve, the dry granules were screened and sizing (The granules were evaluated for various parameters, including compressibility, angle of repose, flow rate, moisture content and particle size distribution). The granules were mixed with Sodium Starch Glycolate, Magnesium Stearate, and Colloidal Silicon dioxide using a double cone mixer (DCM). The granules were then examined after being compressed in a single punch tablet press and blistered (23).

Table (1): Formulation of paracetamol tablets

Ingredients	mg/ tablet	Function
Paracetamol	500	API
Maize starch	85.5	Filler
Chitosan nanoparticles	15	Binder
Colloidal silicon dioxide	12	Glidant
Magnesium stearate	2.5	Lubricant
Sodium starch glycolate	25	Disintegrate agent
Total	640	

Statistical analysis

The results for the analyzed parameters were expressed as mean ± standard deviation (SD). Differences between group means were evaluated using one-way Analysis of Variance (ANOVA) performed with SPSS software version 23.1. Statistical significance was determined at a probability level of $P \leq 0.05$ (24).

Result and Discussion

Preparation of chitosan nanoparticles

Chitosan nanoparticles were synthesized using the chemical method within 24 hours. The formation of inter- and intramolecular cross-linkages, facilitated by a cross-linker, precipitate the chitosan nanoparticle molecules. Glutaraldehyde cross-linker solution was added to the chitosan solution under magnetic stirring at room temperature to prepare the nanoparticles (25). First, a clear solution was observed when both chitosan and glutaraldehyde were dissolved in acidic media and organic media respectively, whereas aggregates were formed spontaneously when a cross linking process started after adding the cross linker solution. Yellowish white particles were precipitated and examined for their shape, morphology, crystalline structure and chemical structure.

Characterization of chitosan nanoparticle

Field Emission Scanning Electron Microscopy (FESEM)

FESEM is used for the characterization morphology and size of the prepared nanoparticles, Figure 2 FESEM micrograph of chitosan nanoparticles shows the spherical shape, uniform and well dispersed of the prepared nanoparticles with a diameter of about 41 to 74 nm, similar to previous studies (26-28). the uniform polymeric distribution of the nanoparticles within the matrix suggests the successful formation of polymeric networks. There are two possible reasons for this behavior. First, the observed structural formation may result from the cross-linking and stabilization processes facilitated by glutaraldehyde and surfactants, respectively. Second, the high surface energy associated with the small particle size may contribute to physical aggregation.

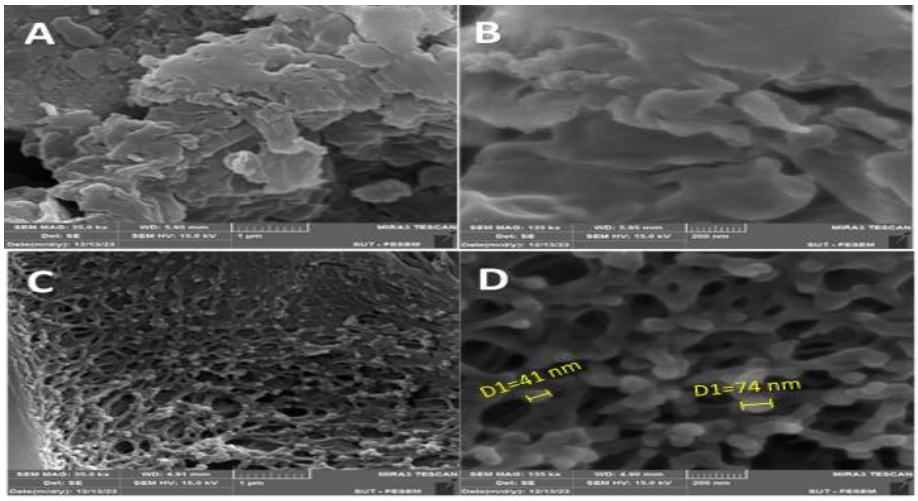

Figure (2): FESEM images of chitosan and the prepared chitosan nanoparticles, A) chitosan at lower magnification, B) chitosan at higher magnification, C) chitosan nanoparticles at lower magnification, D) chitosan nanoparticles at higher magnification

Atomic Force Microscope (AFM)

AFM is widely utilized for its high spatial and vertical resolution, making it invaluable for characterizing the morphology of particles and as a powerful tool for surface topography imaging. Figures 3 depict AFM images illustrating the topography of chitosan and chitosan nanoparticles. Various parameters are used to quantify surface roughness, such as the root mean square (RMS) roughness, which can be calculated from cross-sectional profiles or surface area analyses (29). The RMS roughness obtained by chitosan was 18.6 nm, while RMS obtained by chitosan nanoparticles was 1.15 nm. The magnitude decreased in RMS roughness of chitosan nanoparticles compared to chitosan is attributable to the decrease in size of particles. AFM analysis shows the decrease in particle size for the prepared nanoparticles 62 nm similar to (30) in comparison with 178 nm for chitosan, and also an increase in total number of particles per mm^2(density). The increase in particle density (number of particles per mm^2) observed in the AFM analysis can be explained by the significant reduction in particle size. When the particle size decreases, the surface area occupied by each particle becomes smaller, allowing more particles to be accommodated within the same area.

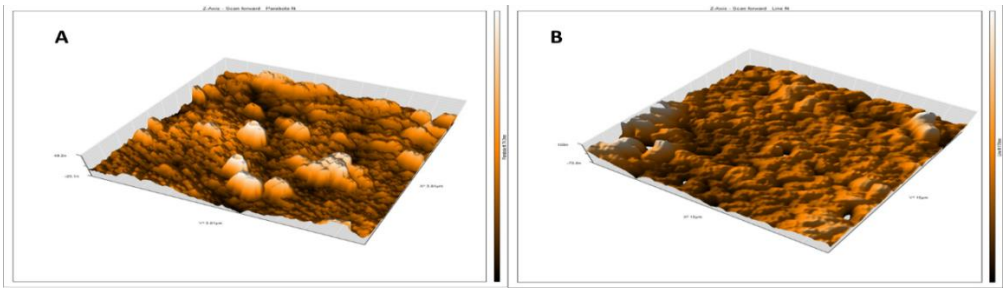

Figure (3): AFM images of, A) chitosan, B) chitosan nanoparticles

Fourier Transform Infrared spectroscopy (FT-IR)

The FT-IR analysis of chitosan and chitosan nanoparticles, presented in Figure 4, reveals significant spectral changes. The FTIR spectrums, broad peaks at 3412-3420 cm^{-1} attributed to O-H and N-H stretching vibrations was

observed for chitosan and chitosan nanoparticles respectively. In nanoparticles, the peak intensity decreased, suggesting crosslinking of amino groups with glutaraldehyde. Furthermore, the 2918 cm^{-1} and 2923 cm^{-1} bands for chitosan and chitosan nanoparticles respectively, corresponds to the stretching vibrations of C-H group, no substantial changes were observed indicating that the carbon chain of chitosan remained largely unaffected. The characteristic amide I, II and carbonyl bandsC=O near 1653 and 1592 cm^{-1} for chitosan and 1658 and 1654 for the nanoparticles (C=O stretching) became more intense and slightly shifted in the nanoparticles spectrum, indicating the formation of Schiff bases (C=N bonds) due to reaction between glutaraldehyde and amine groups. Minor shifts and intensity changes were observed in the 1260-1421 cm^{-1} region for chitosan and 1254- 1409 cm^{-1} region for the prepared nanoparticles, slight change were observed, indicating a minor modification in the chemical environment of the methyl groups. Additionally, the bands 1075-1152 cm^{-1} region for chitosan, 1072-1150cm^{-1} region for the nanoparticles, corresponding to C-O-C stretching, confirming slight changes in the polysaccharide backbone after nanoparticle formation (26, 31).

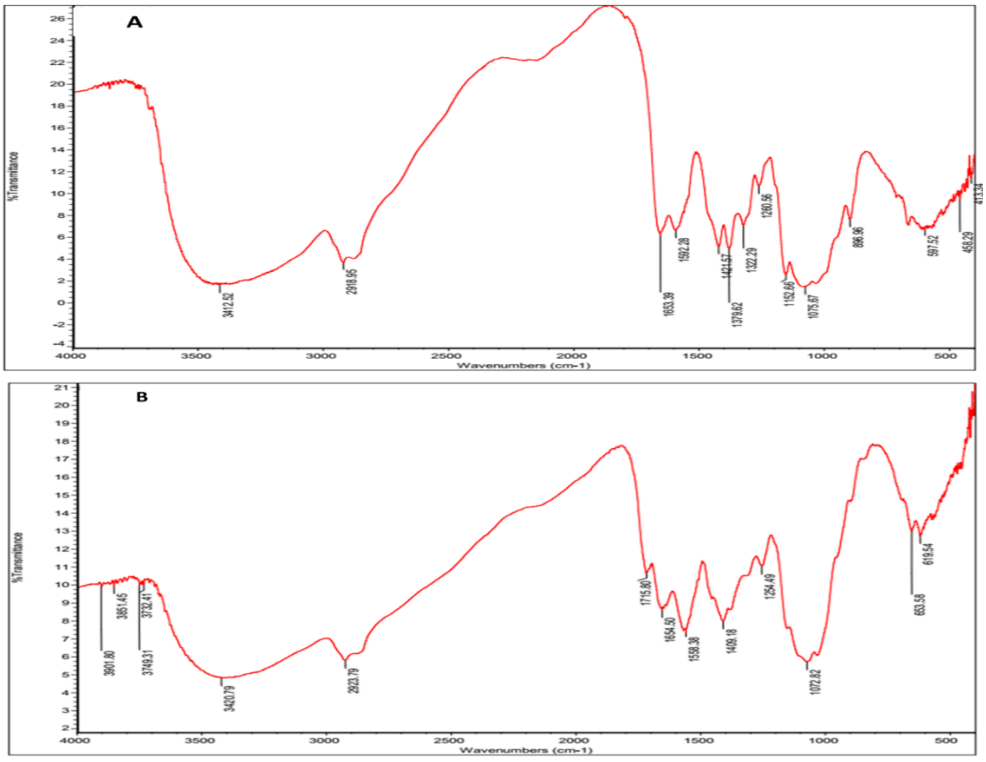

Figure (4): FTIR spectrum of the A) chitosan and B) chitosan nanoparticles

X-Ray Diffraction (XRD)

The XRD technique was employed to find out the crystalline structure of the chitosan and prepared chitosan nanoparticles as shown in Figure 5, the XRD patterns of the original chitosan powders exhibited a characteristic sharp peak at 2Ø of about 20° indicating the high degree of crystallinity of chitosan. Moreover, no additional peaks appear that indicate the chitosan possesses high purity. These results are in agreement with many previous studies (32, 33). XRD patterns of chitosan nanoparticles show a broad peak at 2Ø of about 20° in

compression with the sharp peak identified for original chitosan powder, explaining that the crystalline structure of chitosan is destroyed by cross-linking interactions between the amino groups on chitosan and glutaraldehyde (34, 35). Resulting in an increase in the broad of the characteristic peak of chitosan and indicating a decrease in the crystallinity degree or amorphous character (36). Through bragg low the crystallization of chitosan and prepared chitosan nanoparticles estimated by Braggs equation: **$n\lambda = 2d\sin\theta$**

Where, θ is the beam diffraction angel with respect to the crystalline plane, n is integer number, λ is the wave length of X-Ray incident beam and d is distance between the entire structural planes. In this study, Bragg's equation was used to estimate the interplanar spacing (d-spacing) of chitosan and chitosan nanoparticles. The results revealed that the crystallization of chitosan nanoparticles reached 1.58 Å, while in chitosan, it was 4.36 Å.

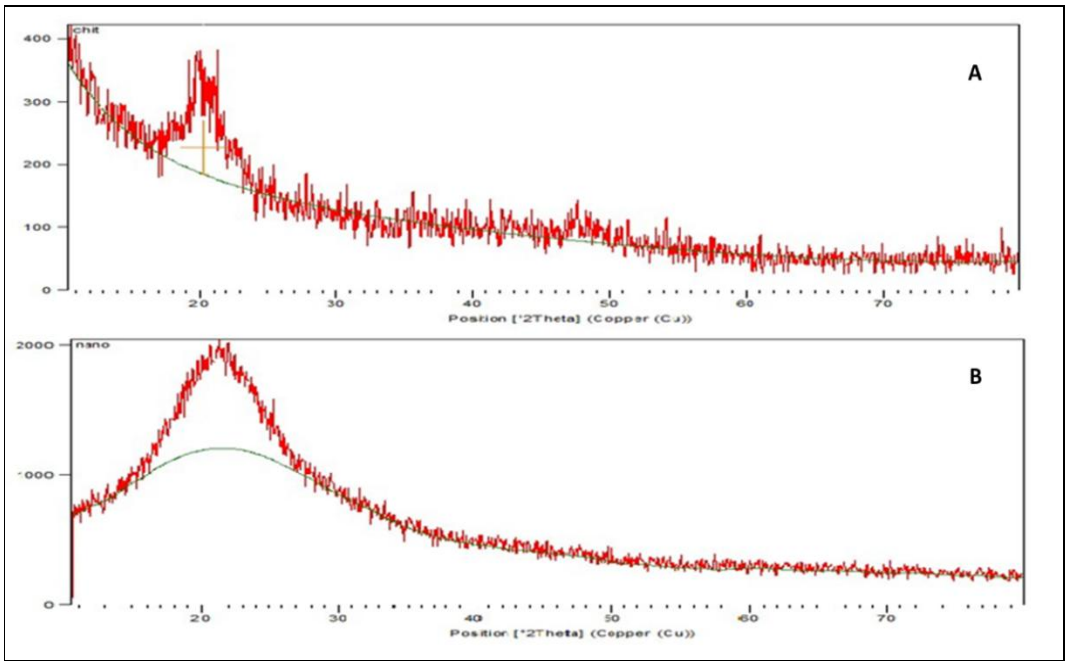

Figure (5): XRD patterns of A) chitosan, B) chitosan nanoparticles

Formulation of paracetamol tablets with chitosan nanoparticles

As per the data obtained by the experiment, a combination of chitosan nanoparticles, chitosan and maize starch showed good binding and disintegrating properties as compared to the commercial paracetamol tablets. The various micrometric characteristics and flow properties of the granules obtained by wet granulation showed variation in their values. The values of the physical properties of the two formulas are shown in Table 2. Angle of repose, bulk density, tapped density, hausner's ratio, and compressibility index were all calculated for granules pre-compression. All of the methodologies mentioned in pharmacopoeias were used to carry out the evaluation (37).

To determine the bulk density (ρb), the volume of known quantity before tapping were measured, while the tapped density (ρt) was determined by measured volume after tapping. Furthermore, carr's index and hausner's ratio were used to determine the compressibility and flowability properties of the granules which were calculated from the equations

below(38). Carr's Index = [(ρt–ρb/ρt)] ×100

$$\text{Hausner ratio} = \rho t/\rho b$$

Hausner ratio and Carr's index compressibility are shown in Table 2. The compressibility of granules was measured to identify their ability to compact and reduce in volume when pressure is applied. This is required to guarantee that the granules are suitable for tableting in order to generate a high hardness (pressure-resistant) tablet. Compressibility index is also an indicative of the flow properties of granules while Hausner ratio relates to the cohesiveness of the granules (39). When the percentage of carr's index compressibility is lower than 15%, the granules have high flowability properties while cohesive granules have carr's index compressibility percentage of more than 25% indicating low flowability properties (40, 41). Granules with Hausner ratio less than 1.25 have high flowability properties (42) and granules with angle of repose preferably less than 30º means good flow (43), while granules with 30º and more would flow with difficulty (44).

Physical properties of the tablet (post compression) parameters were evaluated for commercial and prepared tablets including weight variation, hardness, friability and disintegration, as showed in Table 3

Our study demonstrated that the average weight of both the commercial and prepared tablets was within the limits identified by the USP, with a deviation of ±5%. Thus, incorporation of chitosan nanoparticles to the formulation did not affect in tablet weight appreciably. The small variation in weight indicate high homogeneity and high followability among the produced granules. Various factors can influence tablet weight, such machine speed, powder flow properties and granule density and particle non-uniformity during the tablets preparation, also the type and amount of excipients all of which can lead to weight variation in tablets (45). our finding aligns with the study by Abdulla and Oshi (46)., who demonstrated that the weight variation of paracetamol tablets (Amidol and Panadol) remained within the acceptable range as per the USP standards for tablet weight. Furthermore, their research observed that the incorporation of croscarmellose sodium, rather than microcrystalline cellulose, into the commercial tablet formula did not result in a significant change in tablet weight.

Tablet hardness is generally influenced by factors such as the quality of the binder, tablet diameter and compression force (47). Therefore, in the present study, the prepared tablets exhibited superior hardness properties compared to the commercial tablets. The incorporation of chitosan nanoparticles provided enhanced binding capabilities in comparison to the binder used in the commercial tablets (PVP K-30), leading to an increase in hardness. This result highlights the effective binding properties of chitosan when combined with maize starch. Chitosan forms hydrogen bonds with starch molecules, which increases interparticle attraction, resulting in a more compact and mechanically stronger tablet. These findings are in line with the study by Yarangsee *et al.* (47), who observed that the homogeneous distribution of chitosan nanoparticles into the hydrated kaolin structure in the feed suspension improved the flowability and provided optimal tablet hardness.

The current study revealed a significant difference in the friability values between the two types of tablets. According to USP standards, a

maximum weight loss of no more than 1% during the friability test is generally considered acceptable. In our results, all tablets met the acceptable limits and successfully passed the friability test, however the prepared tablets exhibited lower friability compared to the commercial tablets. This reduction in friability can be attributed to the presence of binding agents. Specifically, the incorporation of chitosan nanoparticles into the paracetamol tablet formulation contributes to a decrease in friability due to chitosan's effective binding properties. Chitosan enhances particle cohesion within the tablet formulation through electrostatic interactions and hydrogen bonding. These interactions strengthen the binding between particles, thereby improving the friability performance of the tablets.

Disintegration time is a critical physical property of solid dosage forms, representing the time required for tablets to break down into smaller particles. This parameter is essential for ensuring dissolution and may significantly influence the rate of drug absorption. In the present study, the average disintegration time for both commercial and prepared tablets was found to be 4 minutes, with no significant difference between the two tablet types. Consequently, the incorporation of chitosan nanoparticles into the paracetamol formulation did not significantly affect the disintegration time, due to that the disintegration time may vary based on the disintegrator used (sodium starch glycolate) being used in this study. The data obtained from this study indicated that both the commercial and prepared tablets exhibited disintegration times within the acceptable limit of not exceeding 30 minutes as stipulated by the USP. These findings are consistent with previous studies that measured the disintegration times of paracetamol tablets from various brands, which typically ranged from 51 seconds to 10 minutes (48-51).

Table (2): Physical properties for commercial granules and prepared granules using chitosan nanoparticles.

Test	Commercial paracetamol	Paracetamol chitosan nanoparticles
Bulk density (g/cm^3)	0.81	0.84
Tapped density (g/cm^3)	0.86	0.88
Carr's index %	5.8	4.5
Hausner's ratio	1.06	1.04
Angle of repose (degrees)	28.19	26.44

Table (3): Comparison between commercial paracetamol and chitosan nanoparticles paracetamol in physical and chemical properties

Test	Commercial paracetamol	Paracetamol chitosan nano-particles
Weight variation (mg)	640 ± 17	640 ± 11
Hardness (N)	140±0.44 *	152±0.09*
Friability %	0.3±1.76*	0.2±1.98*
Disintegration (min)	4±3.99	4±4.09
API concentration % (HPLC)	100.1±3.03	103.1±3.03

⁎ = Significant difference at p≤ 0.05.

The paracetamol assay is conducted to determine the concentration of the active pharmaceutical ingredient (API) in the tablets using the High-Performance Liquid Chromatography (HPLC) method. According to the

United States Pharmacopeia (USP) monograph, the acceptable limits for paracetamol assay are not less than 90% and not more than 110% of the labeled amount (500 mg). The mobile phase was passed through the column until a constant pressure and stable baseline were achieved. The reference standard was injected, and the area under the curve at the retention time of 6 minutes was integrated. Subsequently, test solutions of both the prepared and commercial tablets were injected to determine their concentrations. The paracetamol concentrations obtained from 20 randomly selected tablets of commercial and prepared formulations were found to be 100.1% and 103.1%, respectively. These results indicate that both tablet types contained paracetamol concentrations greater than 90% and within the limits specified by the USP, as shown in Figure 6. No significant difference was observed between the two tablet types, due to the paracetamol concentration is primarily influenced by the quality of the paracetamol used. These findings are consistent with Masheta *et al*. (52), who evaluated the concentration of (API) in various paracetamol brands manufactured in Iraq, including Paracetol (SDI Co), Safacetol (SAFA Co), and Omol (NP Pharma Co), with concentrations recorded at 107.8%, 105.6%, and 105.0%, respectively.

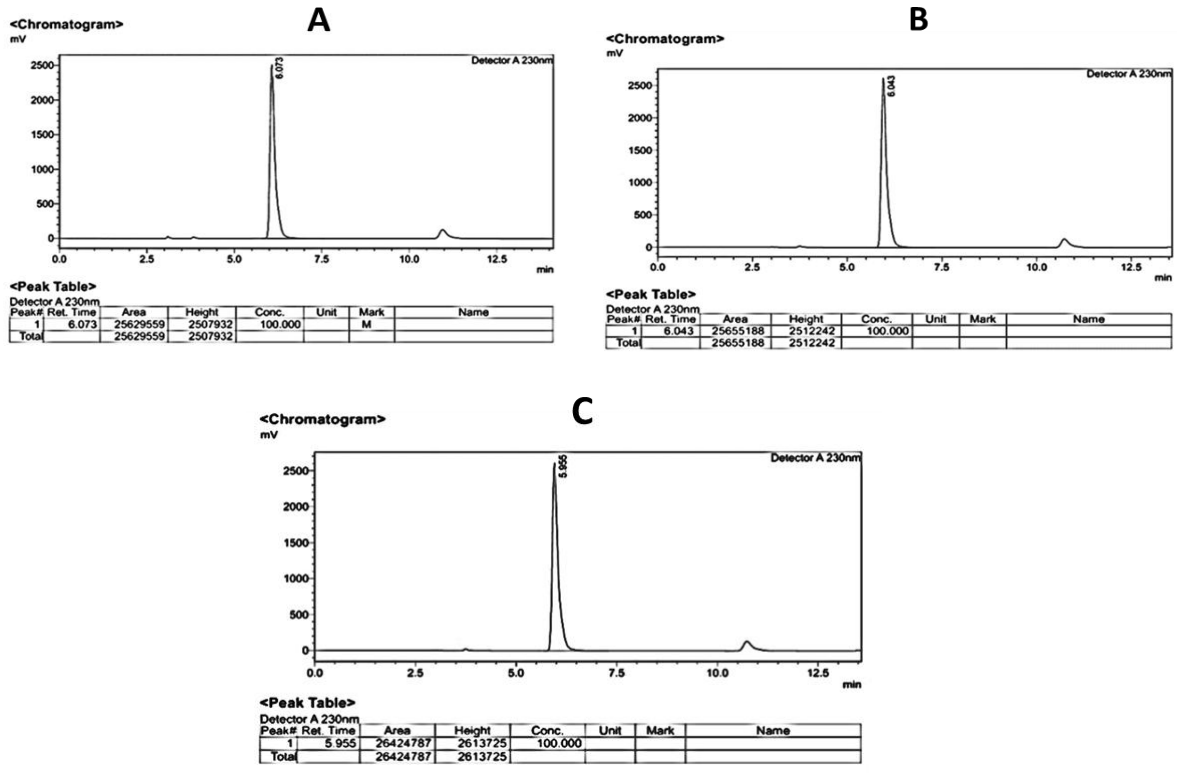

Figure (6): HPLC chromatogram A) Paracetamol standard, B) Test solution of commercial tablet and C) Test solution of prepared tablet

In-vitro dissolution profiles comparing two types of tablets, the prepared formulas and commercial product (commercial tablets, Samarra Pharmaceutical Factory) from six different samples were evaluated in a pool dissolution. In the pH 1.2 HCl dissolution medium, the maximum drug

release (Q) from commercial and prepared tablets was 102.1% and 103.2%, respectively, within 30 minutes, as shown in Figure 7. When tested in the pH 4.5 acetate buffer, the fastest release was observed for the prepared tablets, which completely dissolved within 18 minutes, reaching a maximum Q of 104.8%. In contrast, the commercial tablets released 103.7% of the drug in 27 minutes, as shown in Figure 8. In the pH 5.8 phosphate buffer, the release profile revealed that the prepared tablets were fully dissolved within 16 minutes, achieving a maximum Q of 100.4%, compared to 101.3% for the commercial tablets, which dissolved in 25 minutes, as shown in Figure 9. A significant reduction in the time required for drug release was observed for the prepared tablets, suggesting that the incorporation of chitosan nanoparticles may enhance the dissolution rate. This is likely due to the smaller particle size, larger surface area, and potentially improved wettability of the chitosan nanoparticles. Such enhancements could contribute to more efficient drug absorption in the intestinal tract, where the majority of absorption occurs. Moreover, Chen *et al*. (53) developed a drug delivery system for prednisolone drug using prednisolone-loaded chitosan nanoparticles for the treatment of pediatric asthma, the study demonstrated that the incorporation of chitosan nanoparticles significantly enhanced the solubility of the drug, resulting in a rapid drug release of 98.5% within 30 minutes(54-56).

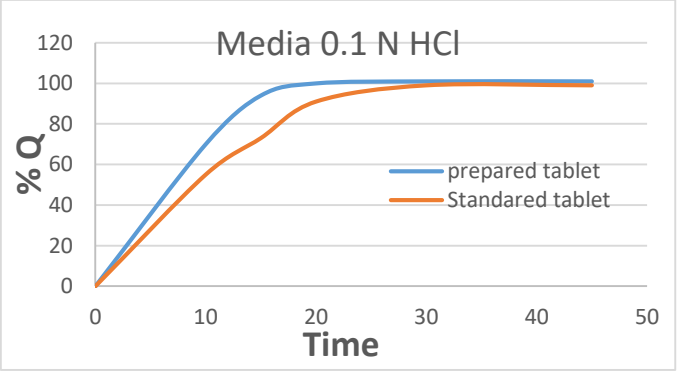

Figure (7): Release profile comparison in dissolution media of pH 1.2

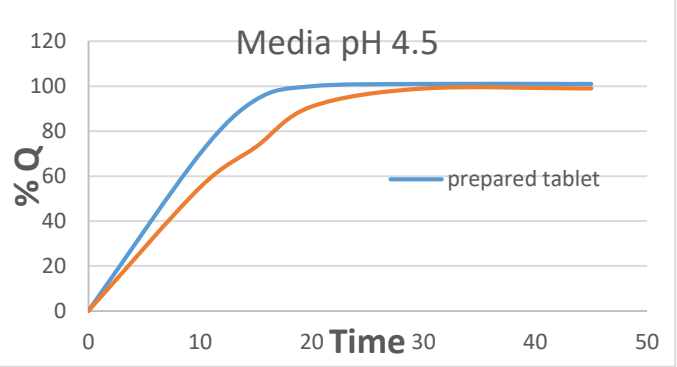

Figure (8): Release profile comparison in dissolution media of pH 4.5

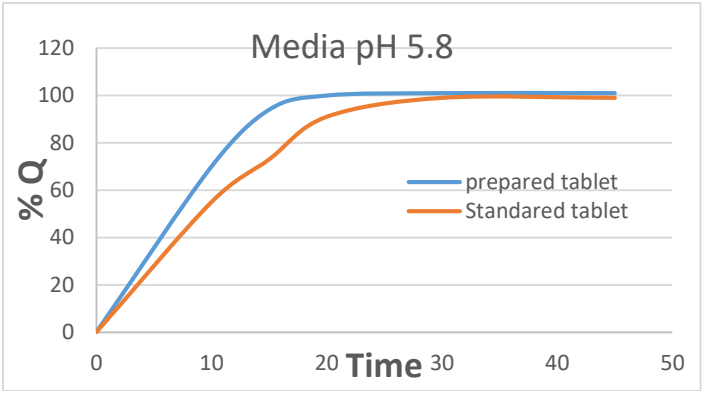

Figure (9): Release profile comparison in dissolution media of pH 5.8

Conclusion

Based on the results, chitosan nanoparticles prepared via the chemical method, were successfully used to improve paracetamol tablets. The nanoparticles, with a size range of 41–74 nm, enhanced binding, disintegration, and biodegradability. Paracetamol tablets formulated with these nanoparticles showed improved hardness and reduced friability compared to commercial tablets. In-vitro release tests demonstrated nearly complete drug release within 16–20 minutes, highlighting the potential of chitosan nanoparticles for enhancing drug bioavailability and immediate release.

References

1. Haas, H. (1983). History of antipyretic analgesic therapy. The American Journal of Medicine, 75(5), 1–3.
2. Przybyła, G. W.; Szychowski, K. A. and Gmiński, J. (2021). Paracetamol—An old drug with new mechanisms of action. Clinical and Experimental Pharmacology and Physiology, 48(1), 3–19.
3. Singh, K. (2023). The shocking truth of paracetamol. Notion Press.
4. Kedir, W. M.; Abdi, G. F.; Goro, M. M. and Tolesa, L. D. (2022). Pharmaceutical and drug delivery applications of chitosan biopolymer and its modified nanocomposite: A review. Heliyon, 8(8).
5. Crini, G. (2019). Historical review on chitin and chitosan biopolymers. Environmental Chemistry Letters, 17(4), 1623–1643.
6. Al-Manhel, A. J.; Al-Hilphy, A. R. S. and Niamah, A. K. (2018). Extraction of chitosan, characterisation and its use for water purification. Journal of the Saudi Society of Agricultural Sciences, 17(2), 186–190.
7. Huet, G.; Wang, Y.; Gardrat, C.; Brulé, D.; Vax, A.; Le Coz, C.; Pichavant, F.; Bonnet, S.; Poinssot, B. and Coma, V. (2023). Deep chemical and physico-chemical characterization of antifungal industrial chitosans—Biocontrol applications. Molecules, 28(3), 966.
8. Elangwe, C. N.; Morozkina, S. N.; Podshivalov, A. V. and Uspenskaya, M. V. (2024). Evaluation of composition effects on the tissue-adhesive, mechanical and physical properties of physically crosslinked hydrogels based on chitosan and pullulan for wound healing applications. International Journal of Biological Macromolecules, 133857.
9. Steglińska, A.; Nowak, A.; Janas, R.; Grzesik, M.; Śmigielski, K.; Kręgiel, D. and Gutarowska, B. (2024). Chitosan as an antimicrobial, anti-insect, and growth-promoting agent for potato (Solanum tuberosum L.) plants. Molecules, 29(14), 3313.
10. Sarfraz, M. H.; Hayat, S.; Siddique, M. H.; Aslam, B.; Ashraf, A.; Saqalein, M.; Khurshid, M.; Sarfraz, M. F.; Afzal, M. and Muzammil, S. (2024). Chitosan-based coatings and films: A perspective on antimicrobial, antioxidant, and intelligent food packaging. Progress in Organic Coatings, 188, 108235.
11. Edo, G. I.; Yousif, E. and Al-Mashhadani, M. H. (2024). Chitosan: An overview of biological activities, derivatives, properties, and current advancements in biomedical applications. Carbohydrate Research, 109199.

12. Mawazi, S. M.; Kumar, M.; Ahmad, N.; Ge, Y. and Mahmood, S. (2024). Recent applications of chitosan and its derivatives in antibacterial, anticancer, wound healing, and tissue engineering fields. Polymers, 16(10), 1351.
13. Asad, K.; Shams, S.; Ibáñez-Arancibia, E.; De Los Ríos-Escalante, P. R.; Badshah, F.; Ahmad, F.; Khan, M. S. and Khan, A. (2024). Anti-inflammatory, antipyretic, and analgesic potential of chitin and chitosan derived from cockroaches (Periplaneta americana) and termites. Journal of Functional Biomaterials, 15(3), 80.
14. Farid, A.; Ahmed, A.; Alaa, O. and Safwat, G. (2024). Desert date seed extract-loaded chitosan nanoparticles ameliorate hyperglycemia and insulin deficiency through the reduction in oxidative stress and inflammation. Scientific Reports, 14(1), 5829.
15. Kumar, M. R.; Muzzarelli, R. A.; Muzzarelli, C.; Sashiwa, H. and Domb, A. (2004). Chitosan chemistry and pharmaceutical perspectives. Chemical Reviews, 104(12), 6017–6084.
16. Badwan, A. A.; Rashid, I.; Al Omari, M. M. and Darras, F. H. (2015). Chitin and chitosan as direct compression excipients in pharmaceutical applications. Marine Drugs, 13(3), 1519–1547.
17. Upadrashta, S. M.; Katikaneni, P. R. and Nuessle, N. O. (1992). Chitosan as a tablet binder. Drug Development and Industrial Pharmacy, 18(15), 1701–1708.
18. Aljebory, A. M. and Alsalman, T. M. (2017). Chitosan nanoparticles. Imperial Journal of Interdisciplinary Research, 3, 233–242.
19. Tiyaboonchai, W. (2003). Chitosan nanoparticles: A promising system for drug delivery. Naresuan University Journal: Science and Technology, 11(3), 51–66.
20. Maitra, A.; Ghosh, P. K.; De, T. K. and Sahoo, S. K. (1999). Process for the preparation of highly monodispersed polymeric hydrophilic nanoparticles [Patent]. Google Patents.
21. Wang, Y.; Wang, X.; Luo, G. and Dai, Y. (2008). Adsorption of bovine serum albumin (BSA) onto magnetic chitosan nanoparticles prepared by a microemulsion system. Bioresource Technology, 99(9), 3881–3884.
22. Mohammed, M. A.; Syeda, J. T.; Wasan, K. M. and Wasan, E. K. (2017). An overview of chitosan nanoparticles and its application in non-parenteral drug delivery. Pharmaceutics, 9(4), 53.
23. Kolling, W. M. (2004). Handbook of pharmaceutical excipients. American Journal of Pharmaceutical Education, 68(1–5), BF1.
24. Laerd Statistics. (2018). One-way repeated measures MANOVA in SPSS Statistics. Statistical tutorials and software guides.
25. Xue, C. (2015). Investigation of chitosan-based materials for sorptive uptake of urea (Master's thesis). University of Saskatchewan.
26. Agarwal, M.; Agarwal, M. K.; Shrivastav, N.; Pandey, S.; Das, R. and Gaur, P. (2018). Preparation of chitosan nanoparticles and their in vitro characterization. International Journal of Life-Sciences Scientific Research, 4(2), 1713–1720.
27. Hadidi, M.; Pouramin, S.; Adinepour, F.; Haghani, S. and Jafari, S. M. (2020). Chitosan nanoparticles loaded with clove essential oil: Characterization, antioxidant and antibacterial activities. Carbohydrate Polymers, 236, 116075.
28. Araujo, J. M.; Fortes-Silva, R.; Pola, C. C.; Yamamoto, F. Y.; Gatlin, D. M.; III, & Gomes, C. L. (2021). Delivery of selenium using chitosan nanoparticles: Synthesis, characterization, and antioxidant and growth effects in Nile tilapia (Oreochromis niloticus). PLOS ONE, 16(5), e0251786.
29. Zainudin, A. A.; Fen, Y. W.; Yusof, N. A. and Omar, N. A. S. (2017). Structural, optical and sensing properties of ionophore doped graphene-based bionanocomposite thin film. Optik, 144, 308–315.
30. Kadhum, W. N. and Al-Ogaidi, I. A. Z. (2022). Evaluation of chitosan–alginate nanoparticle as a stable antibacterial formula in biological fluids. Iraqi Journal of Science, 2398–2418.
31. Matty, F. S. and MohiALDeen, Z. M. (2018). Swelling behavior and drug release of interpenetrating network composed of PVA and chitosan. Ibn Al-Haitham Journal for Pure and Applied Sciences, 31(1), 145–156.
32. Vaezifar, S.; Razavi, S.; Golozar, M. A.; Karbasi, S.; Morshed, M. and Kamali, M. (2013). Effects of some parameters on particle size distribution of chitosan nanoparticles prepared by ionic gelation method. Journal of Cluster Science, 24, 891–903.

33. Almukhtar, J. G. J. and Karam, F. F. (2020). Preparation, characterization and application of chitosan nanoparticles as drug carrier. Journal of Physics: Conference Series, 1664(1), 012071.
34. Antoniou, J.; Liu, F.; Majeed, H.; Qi, J.; Yokoyama, W. and Zhong, F. (2015). Physicochemical and morphological properties of size-controlled chitosan–tripolyphosphate nanoparticles. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 465, 137–146.
35. Zhao, D.; Yu, S.; Sun, B.; Gao, S.; Guo, S. and Zhao, K. (2018). Biomedical applications of chitosan and its derivative nanoparticles. Polymers, 10(4), 462.
36. Patil, P. and Killedar, S. (2021). Formulation and characterization of gallic acid and quercetin chitosan nanoparticles for sustained release in treating colorectal cancer. Journal of Drug Delivery Science and Technology, 63, 102523.
37. Soppimath, K. S.; Kulkarni, A. R. and Aminabhavi, T. M. (2001). Chemically modified poly(acrylamide-g-guar gum)-based crosslinked anionic microgels as pH-sensitive drug delivery systems: Preparation and characterization. Journal of Controlled Release, 75(3), 331–345.
38. Rishabha, M.; Pranati, S.; Mayank, B. and S. P. K. (2010). Preparation and evaluation of disintegrating properties of Cucurbita maxima pulp powder. International Journal of Pharmaceutical Sciences, 2(1).
39. Mohammadi, M. and Harnby, N. (1997). Bulk density modelling as a means of typifying the microstructure and flow characteristics of cohesive powders. Powder Technology, 92(1), 1–8.
40. Endale, A.; Gebre-Mariam, T. and Schmidt, P. C. (2008). Granulation by roller compaction and enteric-coated tablet formulation of the extract of the seeds of Glinus lotoides loaded on Aeroperl® 300 Pharma. AAPS PharmSciTech, 9(1), 31–38.
41. Bacher, C.; Olsen, P.; Bertelsen, P. and Sonnergaard, J. (2008). Compressibility and compactibility of granules produced by wet and dry granulation. International Journal of Pharmaceutics, 358(1–2), 69–74.
42. Panda, D.; Choudhury, N.; Yedukondalu, M.; Si, S. and Gupta, R. (2008). Evaluation of gum of Moringa oleifera as a binder and release retardant in tablet formulation. Indian Journal of Pharmaceutical Sciences, 70(5), 614–618.
43. Reddy, K. R.; Mutalik, S. and Reddy, S. (2003). Once-daily sustained-release matrix tablets of nicorandil: Formulation and in vitro evaluation. AAPS PharmSciTech, 4(4), 480–488.
44. Reus-Medina, M.; Lanz, M.; Kumar, V. and Leuenberger, H. (2004). Comparative evaluation of the powder properties and compression behaviour of a new cellulose-based direct compression excipient and Avicel PH-102. Journal of Pharmacy and Pharmacology, 56(8), 951–956.
45. Farhana, J.; Uddin, M. N. and Islam, M. R. (2018). Comparative in vitro quality evaluation of some paracetamol tablets commercially available in Bangladesh drug market. Indo American Journal of Pharmaceutical Sciences, 5, 527–533.
46. Abdulla, A. A. and Oshi, M. A. (2024). A simple approach to enhance dissolution of commercial paracetamol tablets for fast relief of pain. BrJP, 7, e20240044.
47. Yarangsee, C.; Wattanaarsakit, P.; Sirithunyalug, J. and Leesawat, P. (2021). Particle engineering of chitosan and kaolin composite as a novel tablet excipient by nanoparticles formation and co-processing. Pharmaceutics, 13, 1844.
48. Mosharraf, Z. (2012). Determination of the quality control parameters of paracetamol tablets in Bangladesh pharma market [Unpublished report].
49. Alsaifi, A. and Alyahawi, A. (2018). Quality assessment of different brands of paracetamol tablets in Yemeni market. Universal Journal of Pharmaceutical Research.
50. Gitau, N. S. (2019). Development and evaluation of pediatric orally disintegrating paracetamol tablets (Master's thesis). University of Nairobi.
51. Akhtar, H.; Ali, M.; Ahmad, S. A.; Humayoon, R.; Ahmed, K. Z. and Hassan, H. S. (2022). Assessment of in vitro quality tests of paracetamol brands 500 mg in Karachi, Pakistan. Journal of Pharmaceutical Research International, 34, 11–21.
52. Masheta, D. Q.; Alazzawi, S. K. and Bash, A. A. (2022). Comparative quality control study of widely used brands of paracetamol tablets in Iraq. Maaen Journal for Medical Sciences, 1, 7.
53. Chen, Y.-D.; Liang, Z.-Y.; Cen, Y.-Y.; Zhang, H.; Han, M.-G.; Tian, Y.-Q.; Zhang, J.; Li, S.-J. and Yang, D.-S. (2015). Development of oral dispersible tablets containing prednisolone nanoparticles for

the management of pediatric asthma. Drug Design, Development and Therapy, 5815–5825.

54. Jadou, A. S. and Al-Bahrani, R. (2024). Gold nanoparticles biosynthesized from synephrine extracted from Citrus aurantium peels and its cytotoxicity assay. Iraqi Journal of Biotechnology, 23(2), 139–147.
55. Saeed Ali, Z. A. and Yaseen Al-Araji, A. M. (2024). Effectivity of copper nanoparticle synthesis by Fusarium oxysporum culture filtrate as an antimicrobial agent against Streptococcus thoraltensis and Proteus mirabilis. Iraqi Journal of Biotechnology, 23(3), 194–208.
56. Jasim, H. A.; Fahad, N. K.; Dakhil, O. A. and Ahmed, B. M. (2025). Biosynthesis, characterization and antimicrobial activity of copper nanostructure by palm trunk extract. Iraqi Journal of Biotechnology, 24(Special Issue), 1–6.