RESEARCH ARTICLE

Synthesis and Characterization of New Derivatives of Curcumin and Study of their Biological Activities

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ABSTRACT

Curcumin, a charity for centuries in traditional medicine, was newly shown to possess a broad spectrum of desirable activities. It was creating to be an actual antioxidant and anti-inflammatory agent. Chitosan and its derivatives have several unique properties important in the field of pharmaceutics and medicinal chemistry. The imine or azomethine (–C=N–) functional group is found in Schiff bases. Hugon Schiff was the first to report these compression products of primary amines with carbonyl compounds. Schiff bases are a kind of organic compound with a wide range of uses in analytical, biological, and inorganic chemistry, to name a few. All compounds were studied using Fourier-transform infrared (FTIR), hydrogen-1 nuclear magnetic resonance (HNMR), thermogravimetric analysis (TGA), and differential scanning calorimetry (DSC) apparatuses to determine the thermal stability of derivatives.

Keywords: Chitosan, Curcumin, Schiff base.

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INTRODUCTION

Curcumin, which is derived from the rhizomes of the Curcuma longa plant, has several pharmacological actions, including apoptotic, anti-proliferative (Figure 1), antioxidant, anti-giogenic qualities, and anticancer capabilities, with no noticeable adverse effects. Curcumin has recently been discovered to have potent anti-cancer properties, including melanoma, breast, and prostate cancers.[1] There have been several cases of curcumin being loaded as a medication onto polymers, such as nanogels.[2] Biocompatible, hydrophilic, and low hazardous drug delivery methods are hydrogels made from natural polymers. Hydrogels are also often made from biopolymers like chitosan and alginate. They are most commonly utilized to encase hydrophilic medicines. The polymer sodium alginate is made up of d- mannuronic and acid l- guluronic acid.[3]

Includes two phenolic groups and one 1,3-dikentone group employed for chemical modification (Figure 2) to increase water solubility, plasma solubility, and biological activity. This is not true for every job.

Because the Enol group governs water and plasma solubility, and the bis-keto group is linked to curcumin's

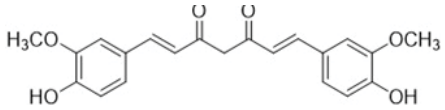


Figure 1: Chemical structure of curcumin

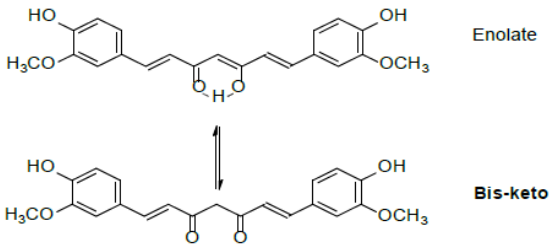
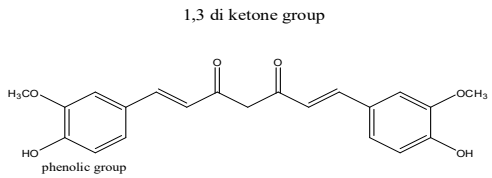


Figure 2: Chemical structure of nolate and Bis-keto



phenolic group and1,3 diketone group in curcmin

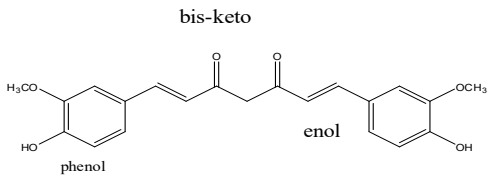


Figure 3: Phenol groups, bis-keto group, and enol group in curcmin

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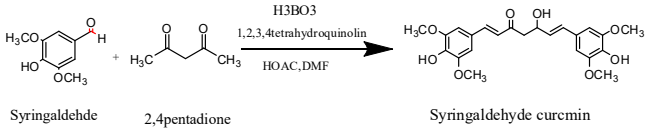


Figure 4: Tautomerism (enolate and Bis- Keto forms)

antioxidant effects, we must preserve the enol group and solely change the phenol and bis-keto groups (Figure 3).[4]

Furthermore, because of active amino and hydroxyl functional groups, chitosan, a polysaccharide biopolymer derivative, exhibits distinctive polycationic, chelating, and film-forming capabilities. Antimicrobial activity, induced disease resistance in plants, and a variety of stimulating and inhibitory behaviors toward a variety of human cell types are only a few of the biological properties of chitosan. Furthermore, because of its inherent antimicrobial characteristics and capacity to distribute extrinsic antimicrobial medications to wounds and burns, chitosan can be utilized to prevent, nor luxury wound and burn infections. Furthermore, it could speed up the actions of inflammatory cells, macrophages, and fibroblasts. Chitosan and its derivatives are also utilized to improve the stability of pharmaceuticals that have been entrapped with chitosan film or chitosan nanoparticles, leading in increased drug growth and toxicity in cancer cells.[5]

Chitosan is a polymer derived from chitin that is commonly used as a cationic ligand. Chitosan, alginate, and combinations of the three have also been employed as bound nanoparticles for coating magnetic units or grafting ligands. In the in vitro setting, sodium alginate grafted magnetic nanospheres were employed as a controlled medication delivery method for Cisplatin. Furthermore, for antibacterial targeted treatment, sodium alginate was employed as a surface modification on magnetic nanoparticles carrying gentamicin. In addition, alginate/chitosan/g-cyclodextrin-coated superparamagnetic nanoparticles were employed to purify the k-amylase enzyme.[6]

Because of these properties, targeted nanoparticles have been considered for therapeutic delivery to cancer cells. Magnetic nanoparticles are employed because an external magnetic field can steer and control them.[7] Drug delivery systems were built in this work based on the cell's features (folate receptors) to create a beset system. Folic acid was employed to bind to it to give chitosan min redox responsiveness and active targeting of folate receptors. Because C-X-C chemokine receptor type 4 (kCXCR4) expression is increased in metastasized breast cancer cells, the major goal of this work was to encapsulate curcumin into nanospheres to improve curcumin efficacy against cancer cells by assessing their vitality (percentage) and the appearance of the kCXCR4 gene.[8]

Schiff bases are made by combining a fun reacted amino group with the carbonyl group of aldehydes or ketones, and they have vimina group properties (-C 14 N-). The antibacterial capabilities of Schiff bases of chitosan with altered aldehydes were described, but there was no convincing justification for their water solubility. Because of their strong metal binding properties, Schiff bases are frequently utilized as ligands in organization chemistry. Schiff bases and their metal complexes

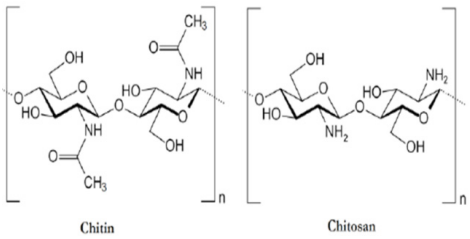


Figure 5: Chemical structure of chitin and chitosan.

have become extremely important because they have antifungal, anticancer, antiviral, antimalarial, and antibacterial properties without being poisonous.[9]

There are free amino groups at the kC-2 site of the chitosan molecule that can negotiate chemical exchange fractions to make various derivatives. When these free amino groups of chitosan react with active carbonyl chemicals like aldehyde or ketone with the produced[10] amine group (–RC=N–) on the mischief-maker product, chitosan Schiff-base is created. Some Schiff-bases of chitosan have been reported to be more effective antibacterial agents than chitosan.[11]

Anti-inflammatory properties Many articles are in the works pertaining to the action of chemicals isolated from C. longa L. that are effective anti-inflammatory inhibitors. Curcuminoids are counterparts of diarylheptanoids and can be classified as such. There are two types of inflammation to be studied: chronic models (cotton pellet and granuloma pouch), in which inflammation and granulomas progress over time (several days), indicating the proliferative phase of inflammation; and acute models, in which anti-inflammatory agents' acute effects on the progression of rat paw edema can be tested.[12]

EXPERIMENTAL

Materials: All chemicals were provided from Merck and Aldrich.

Techniques: Melting points had resolute in open capillary tubes and are uncorrected. FTIR spectra recorded using KBr e discs on a 8400s Shimadzu spectrophotometer and FTIR spectrophotometer, Shimazu (Ir prestige-. (13)1HNMR spectra accepted out by: Bruker, ultra-shield 300 MHz: Switzerland and are reported in ppm, dimethyl sulfoxide (DMSO) used as a solvent.

Preparation of Schiff base[(2S,3S,5R,6R)-2-(hydroxymethyl)-6-methoxy-3-methyl (propylideneamino)tetrahydro-2H-pyran-4-ol] CBR

The derivatives were designed in order to enable for the reporting of a procedure. (14) A gram of chitosan was dissolved in 50 mL of glacial acetic acid (1%) and agitated. A total of 2 hours at 30°C (0.52 gram) propionaldehyde + chitosan The mixture was mixed and cooked for 6 hours in a water bath at 50°C. Acid drops of 5% sodium hydroxide are applied until the desired chemical precipitates. The precipitate was collected and washed numerous times with diethyl ether and methanol to eliminate any leftover

components. The goods were filtered and dried overnight at 60°C in a vacuum oven. The synthesis of Schiff-base is depicted in Scheme 1 as a schematic diagram.

Preparation of Schiff base [4-(((2S,3S,5R,6R)-4-hydroxy-6-methoxy-3-methyl-5-(propylideneamino) tetrahydro-2H-pyran-2-yl)methoxy)-4-oxobutanoic acid]CBRS

In round bottom flask A0.13 gram of anhydrous succinic acid was mixed with the prepared compound(I) dissolved in di-methyl formamide. The mixture was refluxed for 6 hours. A yellowish-white precipitate was obtained. Collect the formed residue and wash it with diethyl ether and dry it in a vacuum oven device at a temperature of 50°C.

Preparation [(2S,3S,5R,6R)-4-hydroxy-6-methoxy-3-methyl-5-(propylideneamino)tetrahydro-2H-pyran-2-yl) methyl (4-((1E,6E)-3-hydroxy-7-(4-hydroxy-3-methoxyphenyl)-5-oxohepta-1,6-dien-1-yl)-2-methoxyphenyl)] CBRSC

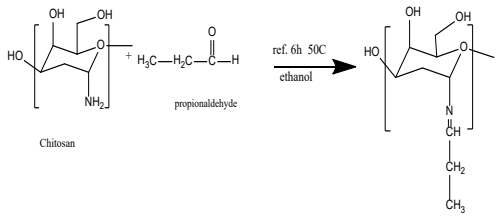
To prepare the derivative (III), it was dissolved in dimethylformamide and then added drops of thionyl chloride to activate the carboxyl group in the compound. The mixture was refluxed for half an hour, and then 0.5 gm of curcumin dissolved with methyl formamide was added. The mixture was refluxed with stirring for 10 hours. On a dark yellow precipitate, wash the product several times with ethanol to dispose of unreacted materials. Dry the product in a vacuum apparatus at a 50°C

Substitution (aspirin) to [((2S,3S,5R,6R)-4-hydroxy-6-methoxy-3-methyl-5-(propylideneamino)tetrahydro-2H-pyran-2-yl)methyl (4-((1E,6E)-3-hydroxy-7-(4-hydroxy-3-methoxyphenyl)-5-oxohepta-1,6-dien-1-yl)-2-methoxyphenyl] backbone

For Substituted the carboxylic drugs, they were dissolved in di-methyl formamide and add drops of thionyl chloride to them, then the mixture was refluxed up for half an hour, and then the derivative(III) was dissolved in di-methyl formamide and mixed with Aspirin the raised for 8 hours. The precipitate formed appeared reddish-yellow, collected and washed with ethanol several times, after which it was dried at a temperature of 50ºC in a vacuum. The method was used to replace medications (ampicillin)

RESULTS AND DISCUSSION

In this study, chitosan was retorted with propionaldehyde to prepare Schiff base compounds this reaction illustrated in scheme below (Schemes 1 and 2).

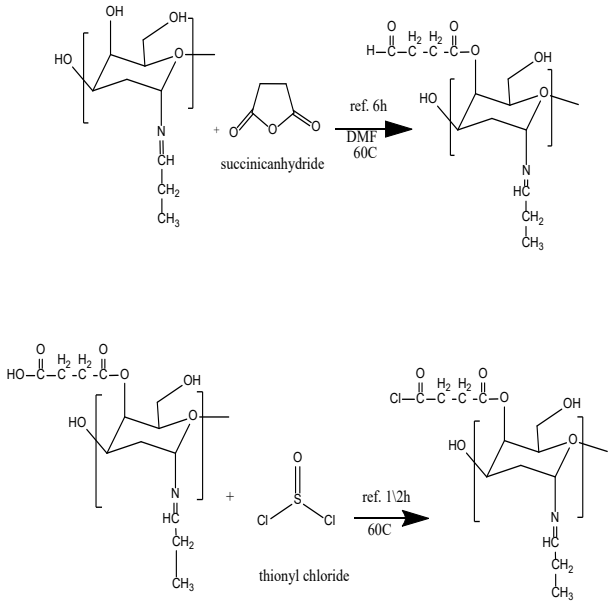


Scheme 1: Reaction of chitosan 1-(propionaldehyde(CBR)

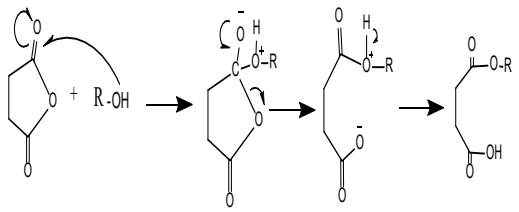
In this investigation, succinic anhydride was utilized as a spacer. Three stages were involved in the Schiff base -g- curcumin reaction with thionyl chloride: The following procedures were described: Steps 1 and 2 are for converting the OH group into a good leaving group, while steps 3 and 4 are for replacing the leaving group with Cl (Scheme 3).

The presence of the (–OH) group in chitosan works as a nucleophilic ring opener. The reaction mechanism, which includes a nucleophilic assault on the carbonyl followed by ring-opening, is depicted below in 3 (Scheme 4).

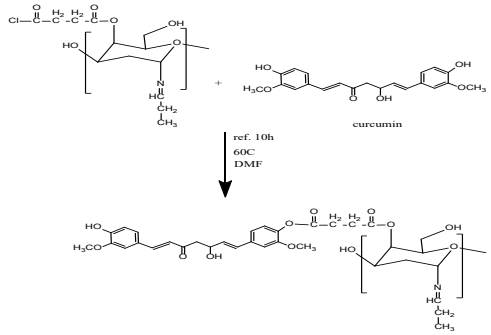
Hydroxyl groups in curcumin reacted with carboxylic group in derivatives (II) to form new natural-synthetic copolymer this reaction illustrated in Scheme 4.



Scheme 2: Ring opening polymerization of succinic anhydride by hydroxyl group in chitosan –Schiff base (CBRS)



Scheme 3: Mechanism of ring opening of cyclic anhydride



Scheme 4: Schiff base reaction of with 1***E***,6***E***)-1,7-bis (4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione ($_{CBRSC}$)

Condensation polymerization of cyclic anhydride on chitosan back bone Schiff base and curcumin carries out could added new properties reacted with carboxylic drug affords both protection than and specific transport properties with longer-acting with the logistic irritation parent drug. reaction of drugs illustrated below (Scheme 5 and 6).

Several derivatives Formulated to improve antimicrobial effectiveness of drugs loaded.

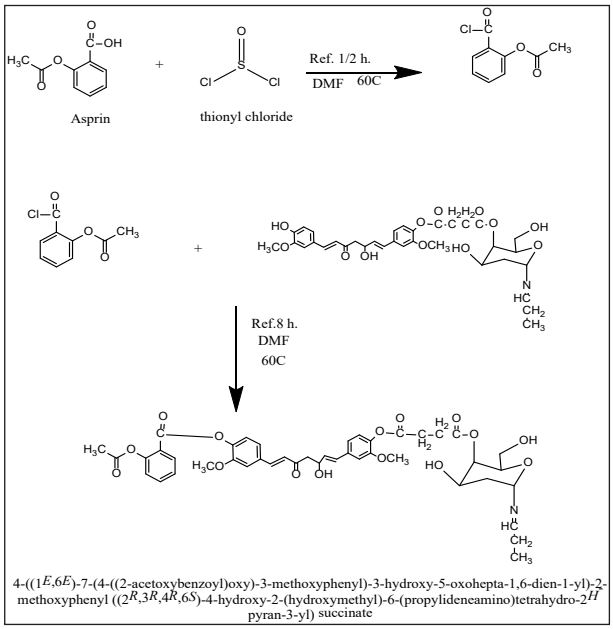
Identification of Prepared Compound by Spectra of FTIR

Derivatives of curcumin showed many FT-IR spectra of all the prepared absorption bands of stretching and bending vibrations of different groups.

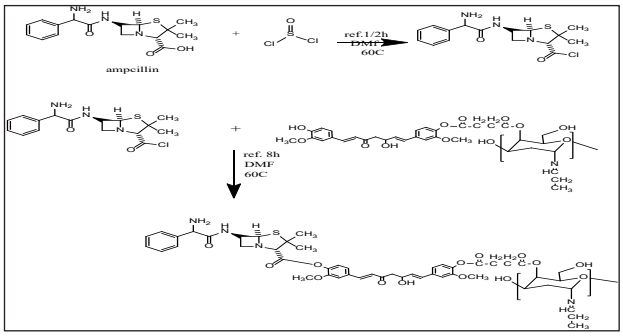
Due to C=N, a band around 1577cm^{-1} was visible in Figure 1. Because of the (CH, CH_2, CH_3) groups, sp3 CH absorption occurs at frequencies less than 3000cm-1 (3000–2840cm^{-1}). The carbonyl of amides stretches at around 1700–1735cm^{-1}, whereas the bands of the carboxylic acid stretch at around 1. In addition, a new general band was developed in all spectra of substances containing ester groups. ^{1}H NMR (ppm): a sharp signal at 2.82 ppm six protons for two CH_3 groups and a sharp signal at 3.82 ppm six protons for N-CH3 groups, two doublet pairs at 6.70–7.75 ppm that attributed to the four aromatic protons and 7.77 ppm for one proton could be attributed to the CH=N 9.70 ppm and 8.62 ppm attributed to the NH and one proton of (OH) carboxylic group (Tables 1 to 3).

Thermogravimetric Analysis (TGA)

Weight is used to calculate thermal treatments for polymers and fractions of the volatile components of the chemical. In the presence of software noise from the device Q600, it does not vary throughout the recording of the soft polymer at a constant pace. As illustrated in Figures 2–7, simultaneous TGA[15,16] analysis is utilized to assess the thermal stability of the nanocomposites produced. The samples are subjected to heat decomposition, resulting in a reduction in the weight of the analyzed samples. Chitosan Schiff base and curcumin



Scheme 5: Substituted of Aspirin to Schiff base derivatives (CBRSCA)



Scheme 6: Substituted of Ampicillin to Schiff base derivatives (CBRSC+ AM)

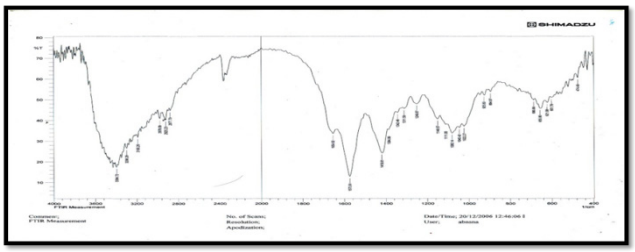


Figure 1: FTIR of CBR.

Table 1: FT-IR spectral of Compounds

No.	*(O-H) cm^{-1}*	*(N-H) cm^{-1}*	*(C-H) cm^{-1} Aliphatic.*	*(C-H) cm^{-1} Aromatic*	*(C=O) cm^{-1} new ester*	*(C-O) cm^{-1}*	*(C=N) cm-^{1}*
CBR	-	-	2982-2873	-	-	-	1577
CBRS	3433	-	2981-2839	-	1728	-	1600
CBRSC	2935	-	2665	3020	1697	-	1627
CBRSC+ ampicillin	-	3460		3047	1720	-	1631
CBRSC+ aspirin	-	3402	2777	3005	1728	-	1689

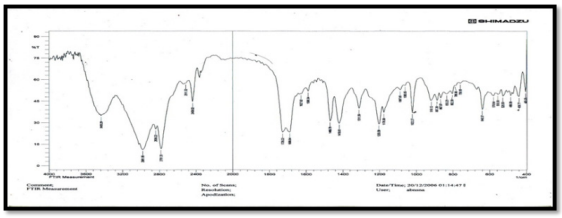


Figure 2: FTIR of CBRS

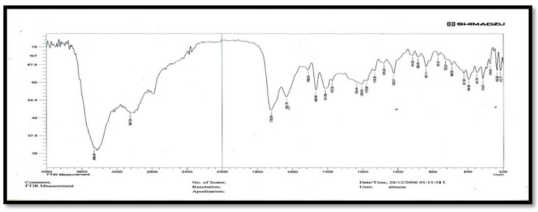


Figure 3: FTIR of CBRSC + ampicillin

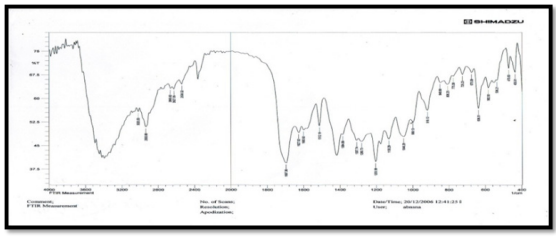


Figure 4: FTIR of CBRSC+Asprin

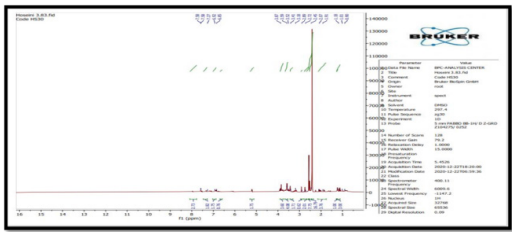


Figure 5: HNMR of CBRSC

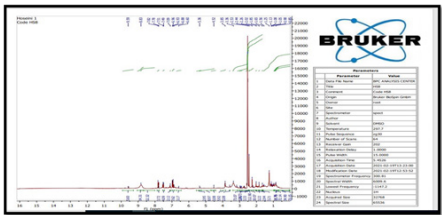


Figure 6: HNMR of CBRSC + aspirin

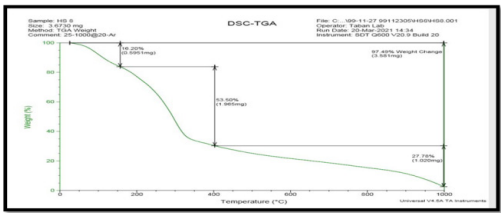


Figure 7: TGA And DSC of CBRSC+ aspirin

Table 2: Physical Properties of Compounds

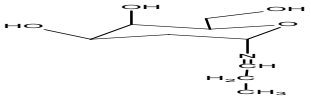
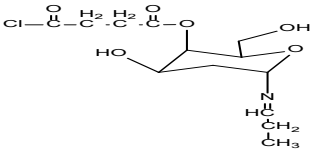
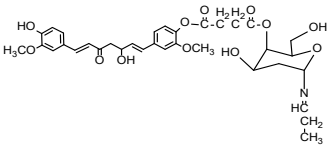
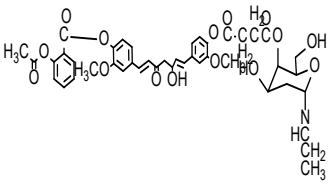
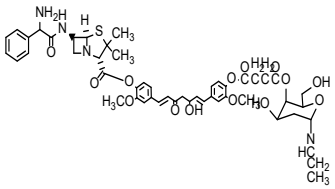
No.	*Compound*	*Colour*	*Softening point ^0C*	*Yield %*
CBR		Transparent white	200-246	90%
CBRS		0ff white	253-274	65%
CBRSC		yellow	283-300	70%
CBRSC+ aspirin		Dark brown	310-325	60%
CBRSC+ ampicillin		Dark brown	334-342	65%

Table 3: Inhibition zones of synthesized compounds

	Antibacterial activity (zone of inhibition in mm) Con.(0.002)				*Antifungal activity (zone of inhibition in mm) Con.(0.002)*
Comps.	*Pseudomonas auroginos*	*Staphylococcus aurus*	*kklebsiella*	*Bacillus*	*Rhizosporium*
CBRSC+Asprin	11	15	22	15	13
Aspirin	15	15	21	15	12
CBRSC+ Amoxicillin	18	13	24	25	17
Amoxicillin	16	27	23	15	17

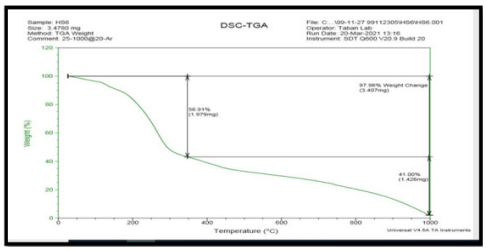


Figure 8: TGA And DSC of CBRSC+ ampicillin

lose roughly 20–27 % of their weight at 400°C and 350°C, respectively (Figure 8).[17]

Antimicrobial Activities

Antifungal activity and antibacterial inhibition zones in mm were scanned alongside antimicrobial properties of chitosan/ propanol Schiff- base curcumin. The antibacterial and antifungal outcomes are shown.[18] The results demonstrate that the bioactivity of all examined substances on harmful bacterial growth differs. Compared to traditional therapies, the produced Schiff- bases in the presence of 2 percentages demonstrate antibacterial activity.[19] The antibacterial effect of the synthesized Schiff- base products is observed compared to the applied standard. It is discovered that most of the curcuminchitosan/ Schiff base/ have positive effects on the growth of both bacteria producing Pseudomonas auroginos, with inhibition zones reaching 22 mm diameters. on bacterial and fungal growth.[20,21] Pseudomonas auroginos and Compound 3 both limit the development of bacteria. Bacillus cereus and Staphylococcus aureus, both Gram +ve bacteria, have inhibition zones of 27 and 23 mm, respectively, whereas Pseudomonas aeruginosa, a Gram -ve bacteria, has inhibition zones of 27 and 27 mm.

CONCLUSION

The present study aims to synthesize and characterize some new chitosan\ Schiff Base, curcumin and substituted with different drugs. Some synthesized compounds gave acceptable FTIR, ^{1}H-NMR that matched data reported in the construct to references. The biological activity for synthesized compounds was estimated to recognize if these compounds will have a medical application.

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