

Synthesis, Characterization, and Biological Activities of Polyglucose Based Hydrazides and their Metal Nano Composites

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Abstract

The synthesis of polyglucose-hydrazide metal nanocomposites is a novel area of chemistry research. Polyglucose metal nanocomposites are widely used for drug delivery to target cancer and other lethal diseases. The major interests of this research were to synthesize, characterize, and find out the antibacterial properties of hydroxyl groups present in polyglucose-hydrazide metal nanocomposites. These nanocomposites were synthesized by acidification, esterification, and hydrazination of glucose and mixing of metal nanoparticles with polyglucose, respectively. The characterization of proposed nanocomposites was done by using scanning electron microscopy (SEM) and, energy dispersive X-ray spectroscopy (EDXS). The biological activities of polyglucose-hydrazides copper, silver and iron nano-composites was tested against *Xanthomonas campestris malvacearum* (a bacterial strain) by agar disc diffusion method. Amongst all, polyglucose-hydrazides copper nanocomposite yielded highest antibacterial activity. Silver and iron nanocomposites also showed good activity. These results indicate that the antibacterial activities of metal nanoparticles are remarkably enhanced by combining with polyglucose hydrazide. These polyglucose-hydrazide metal nanocomposites have great potential as biocompatible antibacterial agents.

Keywords: Hydrazides, Polyglucose, Biological activities, Metal nanocomposites, EDXS.

1. Introduction

The chemical interaction of carbon and nitrogen (C-N) bonds is increasingly becoming important as the foundation for new medication (Dong et al. 2021) and polymer synthesis (Fu et al. 2017). Many scientists have employed these compounds as target structures to determine their diverse chemical synthesis and uses in various fields (Li and Yang 2017). Amide bonds and urea bonds, which are known for their hydrophilic nature (Jalalvandi and Shavandi 2018), are important linkages in polymer blends. Their hydrophilic nature could be attributed to the polar amide linkage (Liu et al. 2016). Hydrazides have an important role in organic chemistry. They possess nitrogen-nitrogen covalent bonds having an acyl group as one of the substituents (Shetty 2018) (NHNH₂ and NHN=CH- groups) with the accessibility of a proton that refers to pharmaceutical importance. Since the invention of isonicotinic acid hydrazide (INH), the potential uses of acid hydrazides and their derivatives have gained momentum as remedial agents. As INH was useful in clinical studies, other heterocyclic hydrazides comprising monocyclic nuclei such as pyrrole, thiophene, furan, and dicyclic nuclei (quinoline as well as isoquinoline) have also been studied (Khan, Siddiqui, and Tarannum 2017). A variety of bioactive compounds contain hydrazide and hydrazone derivatives, which show a range of biological effects. These hydrazides and derivatives exhibit broad activity against bacterial infections and cancer, platelet accumulation, malaria, analgesia, antioxidants (Narang, Narasimhan, and Sharma 2012; Saini et al. 2014), tuberculosis, fungal infections, and viruses.

Antimicrobial activity is the main biological property that has been reported in the scientific literature for this class of chemicals (Popiołek 2017).

The emergence of bacterial resistance to antimicrobial drugs is becoming a major medical concern, especially in nosocomial diseases. Treatment options for these illnesses are typically limited for the elderly and immunocompromised patients (Narasimhan, Kumar, and Sharma 2010) (Butler and Cooper 2011). The discovery of operative and non-toxic antibacterial, antifungal, and chemotherapeutic mediators is still a very significant issue in this regard. (Fang et al. 2006). In 2014, Cui, Z., et al. synthesized and reported antifungal and antitumor properties of monosaccharide and hydrazide derivative-based compounds. Most of the compounds showed better performance than the commercial positive controls in the bioassay test. (Cui et al. 2014). (Liu et al. 2010). In 2000, Sankyo Pharmaceuticals and Nippon Kayaku Co., Ltd. launched acaricides and insecticides containing heteroaryl hydrozone (Kwak and Lee 2018).

Nowadays, there is a growing trend of nanoparticles (Lu et al. 2017) of transition metals that have wonderful applications in all fields like energy storage, electronics, medicine (McDarby et al. 2020), and drug delivery (Prochowicz, Kornowicz, and Lewiński 2017; Rao, Aslam, and Linic 2018; Jamwal et al. 2019). Polymer nano-composites are hybrid organic–inorganic materials (Sun et al. 2019), with at least one dimension of the filler phase of less than 100 nm. Such materials possess tremendous properties (Wang, Tang, and Jin 2019), like light weight (Zhang et al. 2018), greater flexibility (Ananikov 2019; Chen et al. 2018), high surface area (Gao et al. 2020), amazing mechanical strength (Jiang et al. 2015), and remarkable magnetic properties (Coiai et al. 2015). In contrast to conventional composite materials, they offer exceptional properties due to the exceptionally large surfaces of fillers that consume relatively more surface atoms than their equivalent microscale. (Zargoosh et al. 2015). Furthermore, the advancement of nanoscience and nanotechnology opens up new avenues for investigating the bactericidal impact of novel nanomaterials containing metals with high bioactivity, such as silver, copper, and zinc. Bioactive copper nanomaterials are a new class of nanosized antimicrobials that have complementary actions and properties to other nano-sized metals like Ag₂O or ZnO nanoparticles (Dangoor et al. 2021). A variety of polysaccharides are used as polymeric carriers. Among ordinary and semi-synthetic polysaccharides, chitosan, hyaluronic acid, and dextran have received the most attention for pharmacological bioconjugation. Dextran is a naturally occurring polysaccharide composed of monomers of the simple sugar glucose with α-1,6 link and hydroxylated cyclohexyl elements. Because dextran has been approved by the medical community for use as a plasma expander, its popularity has increased. Dextran is decomposable and biocompatible in the blood and gastrointestinal tract (GI). It is not, however, decomposed in lysosomes. It has several hydroxyl groups that can be employed to directly or indirectly bind medicines or proteins (Dangoor et al. 2021; Burcat 2020). Cellulose is the most prevalent organic polymer, with chain lengths ranging from hundreds to millions of glucose units. Glucose, C₆H₁₂O₆, often known as dextrose, exists in three important forms: as a chain fragment, a six-membered ring structure known as glucopyranose, and a five-membered ring structure known as glucofuranose. Starch, the major constituent in many plants such as potatoes, beans, and maize, is another polyglucose natural polymer that is extremely similar. The primary distinction between the two natural polymers is in their structure and biological properties (Burcat 2020)

In this research paper, we have reported the synthesis of polyglucose-hydrazides metal nanocomposites by acidification, esterification, and hydrazination of glucose and mixing of metal (Co, Ag, Fe) nanoparticles with polyhydrazides, respectively. All these polyglucose-hydrazides metal nanocomposites were evaluated for their antibacterial activity against *Xanthomonas campestris malvacearum* by using disc diffusion method.

2. Experimental

2.1 Synthesis of Saccharic Acid

For the synthesis of saccharic acid, 0.1 g of NaNO₃ was added to 15 mL of a 70% concentrated solution of HNO₃ and stirred at 55–60 °C for 20 minutes, followed by the gradual addition of 5 g of anhydrous d-glucose until all of the glucose was brought into the nitric acid. Then the reaction was permitted to proceed for 20 minutes, then stopped by immersing the reaction flask in super-cold water. When the reaction mixture turned greenish, it was stirred and reheated for 90 minutes at 60°C. Then cool it to room temperature, and concentrated KOH was added dropwise to achieve a pH of 9.6. After cooling, 70%

concentrated HNO_3 was added dropwise to bring the solution's pH down to 3.4. The solution was allowed to stand overnight before being washed with chilled water and dried. The product is shown in Figure 1.



Figure 1. Potassium salt of Saccharic acid.

2.2 Preparation of Ethyl Sacchanoate

3g of potassium saccharate were added to 10 mL of ethanol and refluxed. Then a few drops of mineral acid (H_2SO_4) were added to catalyze the reaction. After that, the reaction mixture was stirred for 48 hours at room temperature. The product was centrifuged, washed with distilled water, and then dried at 60°C for 48 hours.

2.3 Synthesis of polyglucose-hydrazide

To 5g of ethyl sacchanoate added 15 mL of hydrazine monohydrate dropwise and refluxed the mixture for 48 hours at room temperature. The excess hydrazine monohydrate was removed using a rotary evaporator.

2.4 Synthesis of metal nanoparticles

The metal nanoparticles of copper, silver and iron were synthesized by hydrazine reduction at room temperature without any inert gas or protective agent. Metal salts were dissolved in 10 mL of deionized water, stirred, and then ethanol and hydrazine were added dropwise. At 70°C , the entire mixture was heated. After 20 minutes, the solution's color changed, and it was heated for an additional hour. A few drops of concentrated NaOH were then added stirred the reaction mixture for 10 minutes. Metal nanoparticles were centrifuged, washed with de-ionized water and ethanol, and oven-dried.

2.5 Preparation of Metal Nanocomposites

Solution Blending:

In this process, the polymer was dissolved in the solvent (deionized water) to get a concentrated as well as homogenous solution, which was vigorously stirred at 100°C for 4-5 hours. After this, metal nanoparticles were added, and, after evaporating the solvent, residual product was collected. The ratio of metal nanoparticles to polymer was kept 1:4. The melting point of resultant polymer metal nanocomposites was 75°C . The proposed structure in the polymer metal nanocomposite is given in Figure 2.

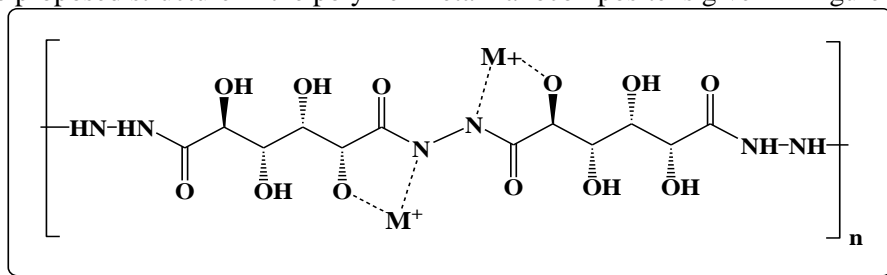


Figure 2. Proposed structure of polymer metal nanocomposite

Melt Mixing:

In this process, polymer was melted at 70°C and powdered metal nanoparticles were added before

being mixed together using a magnetic stirrer. After 20 minutes, it was collected in the sample tubes.

2.6 Biological Study

2.6.1 Antibacterial activity assay of metal nanoparticles

In this trial agar plate was inoculated with *Xanthomonas campestris malvacearum*. 6 mm filter paper disc carrying concentrated suspension (0.1%) of copper, silver, and iron nanoparticles, positive control (antibiotic calomox), and negative control (solvent) were positioned at equal distance from each other on ager plate. Then placed this plate in incubator for 16-18 hours at 37°C.

2.6.2 Antibacterial Activities assay of polyglucose-hydrazide metal nanocomposites

Abovementioned procedure was repeated for antibacterial activity assay of polyglucose-hydrazide metal nanocomposites. Filter paper discs of 6 mm carrying (0.1%) concentrated suspension of each polyglucose-hydrazide metal nanocomposite, positive control, and negative control were placed at equal distance on agar plate. It was incubated for 16-18 hours at 37°C.

3. Results and Discussion

The initial product Saccharic acid was prepared by the reaction of sodium nitrate nitric acid and d-glucose. A vigorous reaction took place during first 15 minutes in which larger portion of glucose was brought into the nitric acid and a light-yellow gas (N_2O_4) evolve which is an indication of reaction's end point. After cooling a greenish color was appeared, which indicate the presence of N_2O_4 . To remove excessive N_2O_4 completely the reaction mixture was reheated. The yield of potassium saccharate obtained was 3 g. In product some other acids like oxalic acid, tartaric acid and succinic acid also formed as byproducts. Number of byproducts depends on the reaction time and temperature. Then the above product (potassium saccharate) was reacted with ethanol in the presence of catalyst to replace potassium moieties and formed an ester bond. After that, to the resultant product of previous reaction (ethyl sacchanoate) hydrazine monohydrate was introduced and the final product polyglucose-hydrazide was achieved. The reaction scheme of polymer synthesis is given in Figure 3. The resultant product was in yellow color and its melting point is 55°C.

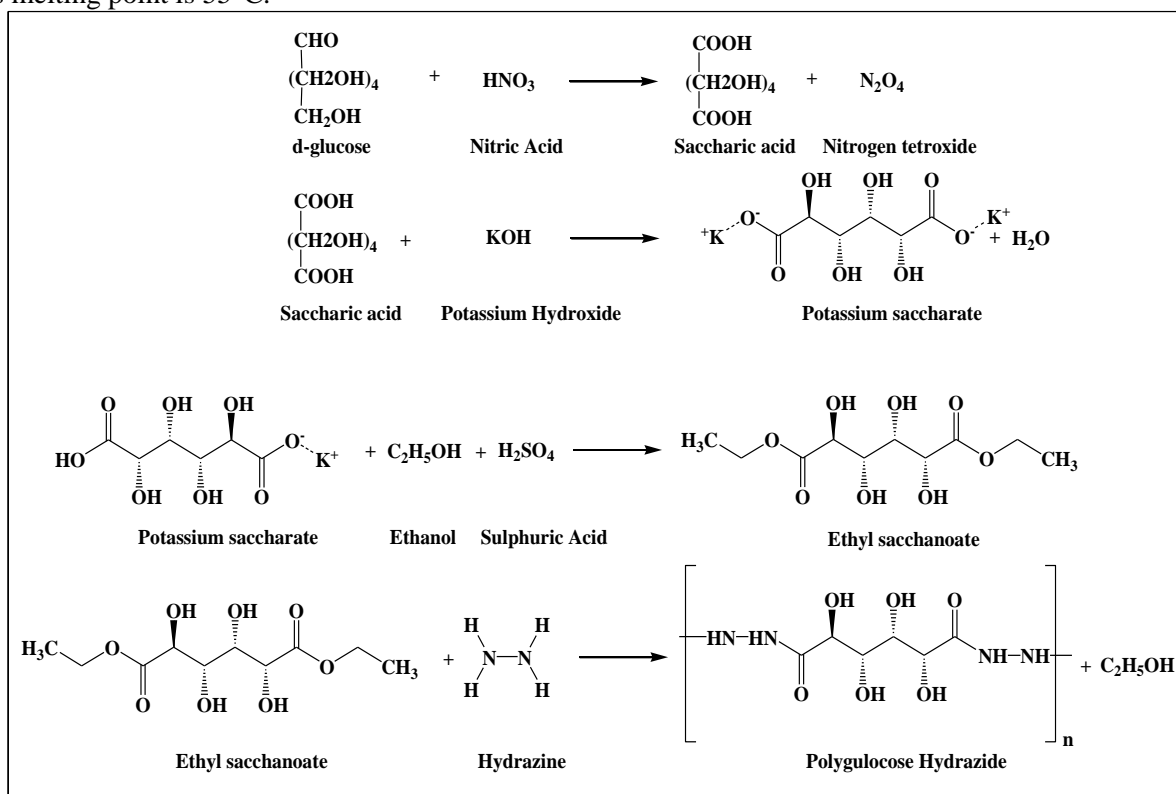


Figure 3. Synthesis mechanism of polyglucose hydrazide.

3.1 UV-Vis Spectroscopy results of polyglucose Hydrazides

For UV-Vis Spectroscopy polymer solution was prepared in deionized water and sonicated for 10 minutes to homogenize it. Polyglucose hydrazide is only soluble in water. Single beam spectrophotometer in 200nm to 800nm range was used. Sharp absorption peak between 380nm to 390nm was observed which indicate the formation of polyglucose hydrazide. The UV- Vis spectrum can be seen in Figure 4.

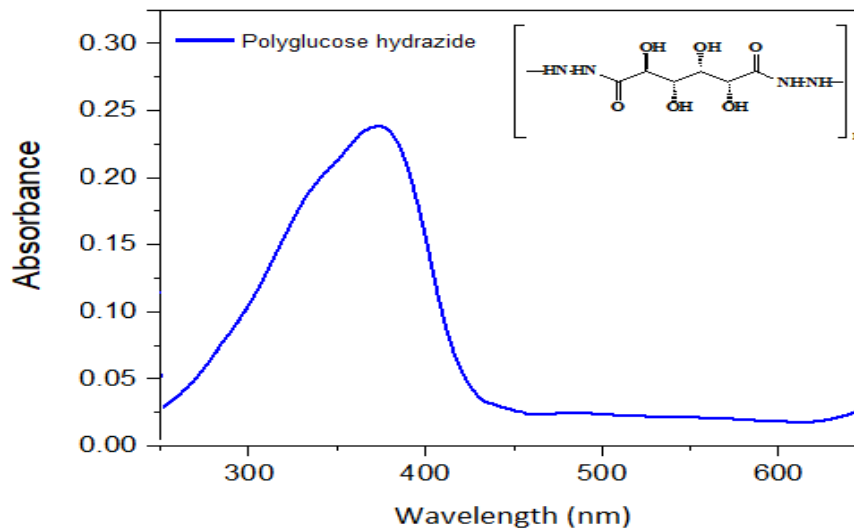


Figure 2. UV-Vis spectra of polyglucose hydrazide.

3.2 SEM results of polyglucose-hydrazide at low and high voltage

SEM images were recorded for the determination of external morphology and size of polyglucose-hydrazide and its metal nanocomposites respectively at high voltage Figure 5(a) and low voltage Figure 5(b). Secondary electrons produced from surface of sample delivers the information of peripheral morphology. Two categories of detectors were used, secondary electron detector and back scattering electron detector.

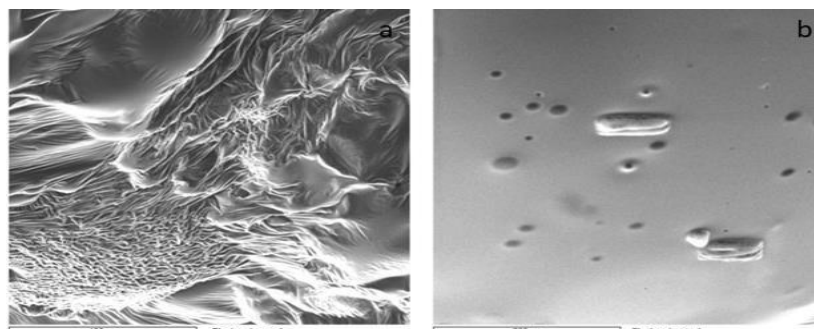


Figure 5. SEM results of polyglucose hydrazides at high voltage (a) and at low voltage (b).

SEM images reveal that polyglucose-hydrazide have very interesting morphological characteristic of interior porous massive microflakes with irregular morphology are randomly arranged. The interior porous network was helpful in adsorption of various colors and target medicines. The size distribution is around 400 µm (Tian et al. 2013).

3.3 SEM result for polyglucose-hydrazide Copper, Iron and Silver Nano-Composites

The SEM results for polyglucose-hydrazide copper, iron and silver nanocomposites are shown in Figure 6 a, b and c, respectively. The SEM image of polyglucose-hydrazide copper nanocomposite reveals that particles have spongy appearance on polymer surface just like the bubbles on surface of a surfactant Figure 6(a). They were spherical and large in size having diameter 200µm. SEM results for polyglucose-

hydrazide iron nanocomposites at high voltage reveals the materials have bubbles on the surface but the size of the bubbles is smaller and material is less spongy as compared to the copper nanocomposites Figure 6(b). While polyglucose-hydrazide silver nanocomposites at high voltage showed comparable morphology to polyglucose-hydrazide copper nanocomposite, Figure 6(c). The SEM images indicates that nanoparticles randomly arranged, spherical shape on surface of polymer material and average diameter is about 200 nm.

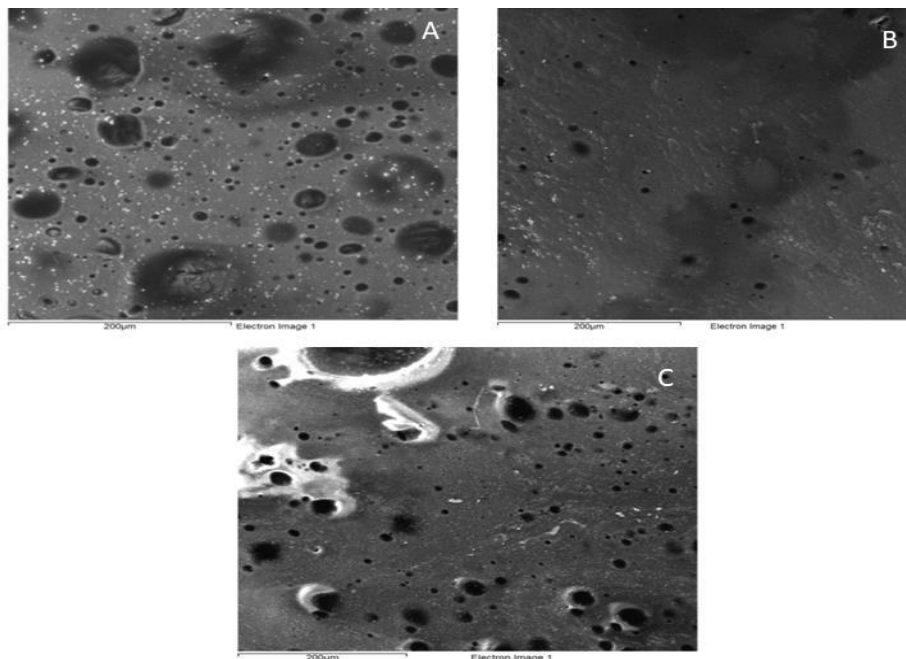


Figure 6. SEM results for polyglucose hydrazide Copper (A), Iron (B) and Silver (C) nanocomposites.

3.4 EDXS results for polyglucose-hydrazide Copper Nanocomposites

EDXS system coupled with scanning electron microscope (SEM) was used to define the atomic percentage of elements present in polyglucose-hydrazide copper nanocomposites. It is clear from spectrum that the energy level for carbon, nitrogen and oxygen were in the range of 0.3, 0.4 and 0.5 respectively. The copper peak appeared at 0.95keV shows loosely bonded copper atoms present at the surface of nanocomposite. The copper peak at 8.1keV shows strongly bonded copper atoms with polyglucose-hydrazide. The atomic percentage was in the following order; carbon: 30.07 % nitrogen: 25.12 % oxygen: 39.24 % and copper: 3.19 %. The EDX spectrum for polyglucose-hydrazide copper nanocomposites is shown in Figure 7.

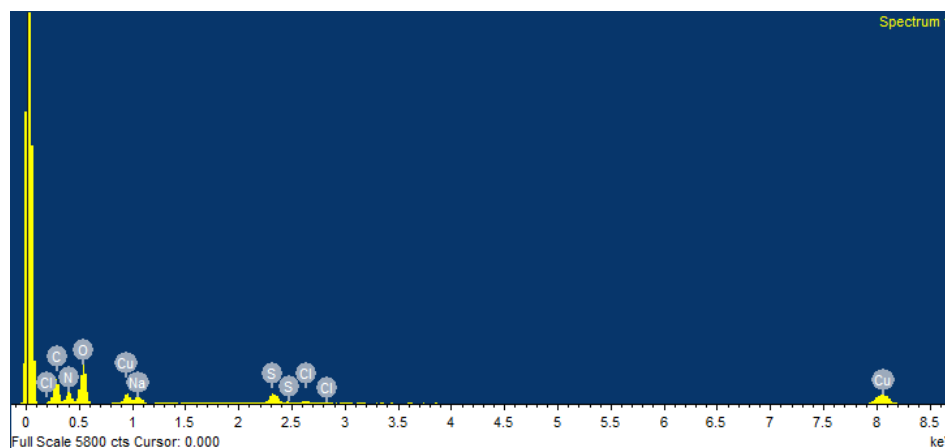


Figure 7. EDX spectrum for polyglucose-hydrazide copper nanocomposites.

3.5 EDXS results for polyglucose-hydrazide Iron Nanocomposites

EDXS results for polyglucose-hydrazide Iron nanocomposites shows that the energy level for carbon, nitrogen and oxygen were in the range of 0.3, 0.4 and 0.5 respectively. The iron peak appeared at 0.7keV shows loosely bonded Iron atoms present at the surface of nanocomposite. The Iron peak at 6.5 and 7.1keV shows strongly bonded Iron atoms with polyglucose-hydrazide in the inner core. The atomic percentage was in the following order; carbon: 36.64 % nitrogen: 20.75 % oxygen: 34.87 % and iron: 3.1 %. The EDXS spectrum for polyglucose-hydrazide Iron nanocomposites is shown in Figure 8.

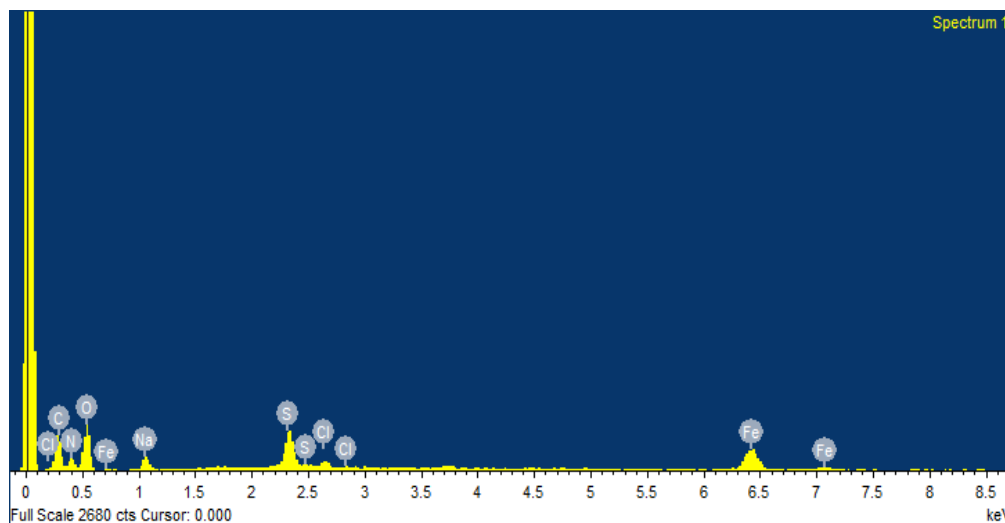


Figure 8. EDX spectrum of polyglucose-hydrazide iron nanocomposite

3.6 EDXS results for polyglucose-hydrazide Silver Nanocomposites

Figure 9 shows EDXS results of polyglucose-hydrazide silver nanocomposites. It is clear from spectrum that the energy level for carbon, nitrogen and oxygen were in the range of 0.3, 0.4 and 0.5 respectively. The silver peaks appeared at 2.6 and 3keV shows aggregate formation with polyglucose-hydrazide. The atomic percentage was in the following order; carbon: 27.98 % nitrogen: 23.82 % oxygen: 46.75% and silver: 0.75%.

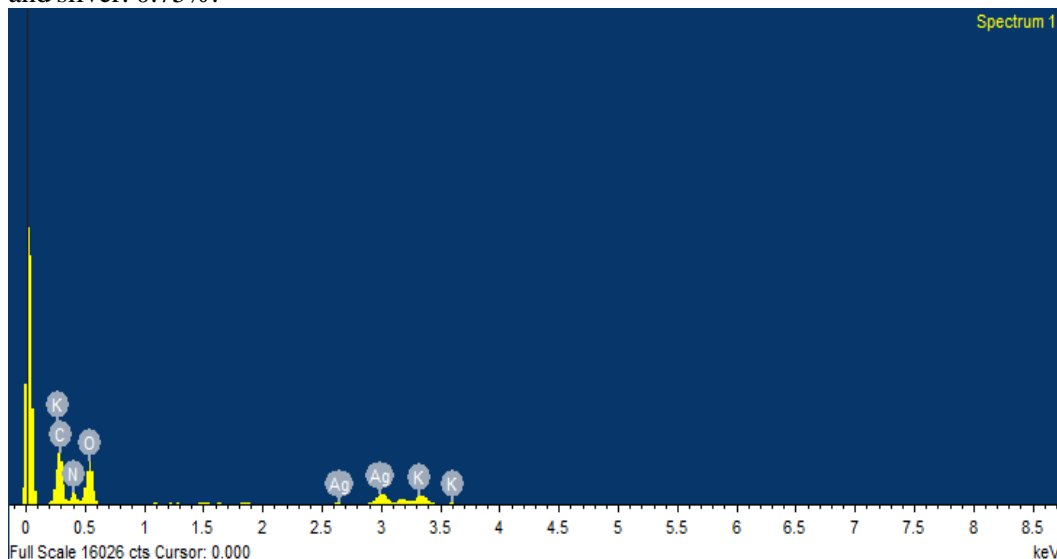


Figure 9. EDX spectrum for polyglucose-hydrazide silver nanocomposites

3.7 Antibacterial activity assay of polyglucose-hydrazide metal nanocomposites

The result of antibacterial activity assays of the metal nanoparticles is listed in Table 1. All the metal nanoparticles showed good antibacterial activities. Copper nanoparticles yielded 14mm inhibition zone while silver and iron showed 12 and 10mm inhibition zone respectively. The results can be seen in Figure 10(a).

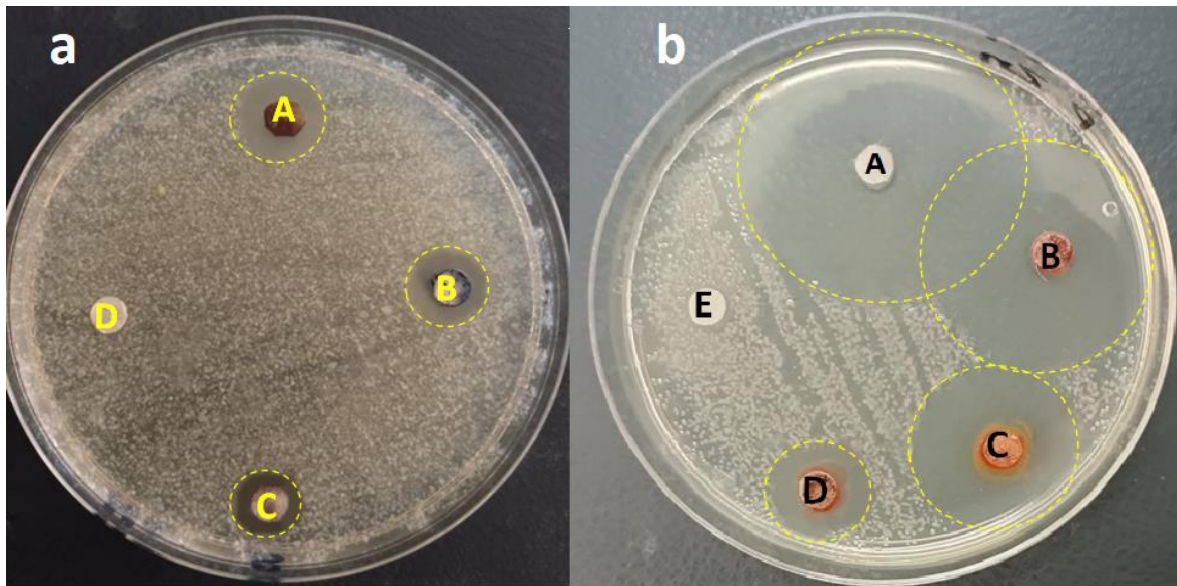


Figure 10. Antibacterial activities of metal nanoparticles (a), and polyglucose-hydrazide metal nanocomposites (b) against *Xanthomonas campestris malvacearum*.

Compared to the positive control, all synthesized products exhibited excellent antibacterial activity for *Xanthomonas campestris malvacearum*. The result of antibacterial activity assays of polyglucose-hydrazide metal nanocomposites is listed in Table 2. Polyglucose hydrazide copper nanocomposites showed 37 mm inhibition zone (82% antibacterial activity), polyglucose hydrazide silver showed 25 mm inhibition zone (55.5% antibacterial activity) and polyglucose hydrazide iron nanocomposite showed 16mm inhibition zone (26.6% antibacterial activity) as compared to the positive control (Calamox) which exhibited 45mm inhibition zone shown in Figure 10(b).

Table 1. Antibacterial activity of metal nanoparticles against *Xanthomonas campestris malvacearum*.

Sr. No.	Code	Sample Name	Zone of Inhibition (mm)
1	A	Cu Nanoparticles	14
2	B	Ag Nanoparticles	12
3	C	Fe Nanoparticles	10
4	D	Solvent (water)	0

Table 2: Antibacterial activity of polyglucose-hydrazide metal nanocomposites against *Xanthomonas campestris malvacearum*.

Sr. No.	Code	Sample Name	Zone of Inhibition (mm)	% Inhibition
1	A	Control (Calamox)	45	--
2	B	Polyglucose-hydrazide copper nanocomposites	37	82
3	C	Polyglucose-hydrazide silver nanocomposites	25	55.5
4	D	Polyglucose-hydrazide iron nanocomposites	16	26.6

5	E	Solvent (water)	0	--
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This antibacterial activity is due to the presence of hydroxyl groups on polyglucose which allows them to interact with the bacterial cell wall. The hydroxyl groups of polyglucose in polyglucose-hydrazide metal nanocomposites are not in conjugation with an unsaturated bond, which engage with the cell wall via intermolecular interactions such as hydrogen bonding and van der Waals contact, the cell becomes destabilized, which can result in bacterial lysis. However, because of their tiny size and increased surface contact with bacteria, polyglucose hydrazide metal nanocomposites can harm the bacteria. The bactericidal mechanism of metal and metal oxide nanocomposites involves the production of reactive oxygen species, including superoxide radical anions, hydrogen peroxide anions, and hydrogen peroxide. These species interact with the bacterial cell wall destroying the cell membrane, which in turn prevents further bacterial growth and causes internal cellular substances to leak out, ultimately causing bacterial death. The results indicate that by combining the polyglucose-hydrazides and metal nanoparticles, antibacterial activities of both materials enhanced.

4. Conclusion

In this research paper, we have reported the synthesis of polyglucose-hydrazides metal nanocomposites by acidification, esterification, and hydrazination of glucose and mixing of metal (Cu, Ag, Fe) nanoparticles with polyhydrazides, respectively. The structural morphology was studied by using scanning electron microscopy at low and high voltage. The SEM images reveal that polyglucose-hydrazide have porous massive microflakes with irregular morphology and size in the range of 400 μ m. While their metal nanoparticles randomly arranged, spherical shape on polymer surface with the size distribution in the range of 200 μ m. Percentage of different elements in these composites was determined by using energy dispersive X-ray spectroscopy. All these polyglucose-hydrazides metal nanocomposites were evaluated for their antibacterial activity against *Xanthomonas campestris malvacearum* by using disc diffusion method. Among these Polyglucose hydrazide copper nanocomposites exhibited 82% antibacterial activity compared to Calamox (Positive control) while silver and iron nanocomposites showed 55.5% and 26.6% antibacterial activity, respectively. This indicates the biocompatibility of as prepared nanocomposites as antibacterial agent.

5. References

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