RESEARCH ARTICLE

Synthesis and Modification of Some New Prodrug Polymers Based on Chitosan and Study of Some Applications

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ABSTRACT

Synthesis of a new various drug delivery systems (DDS) could develop to provide the modifications and improve the therapeutic efficiency and safety of drugs. These may cause a reduction in size and number of doses, side effects, and biological inactivation and elimination. Also, the benefits may include lower toxicity and higher specificity of action

This study includes the preparation of new polymers for chitosan by the interaction of chitosan with different drugs carrying carboxylic groups (cephalexin, ciprofloxacin, amoxicillin, mefenamic acid) after conversion into acid chloride derivatives and diagnosis of the resulting compounds using the FT-IR and HNMR spectrum.

Keywords: Chitosan, Prodrug polymers, Synthesis.

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INTRODUCTION

A polymer is a large molecule consisting of several smaller units named monomers that are bonded together.[1] More specifically, the biopolymer is categorized as the natural polymer result by plants, animals and microorganisms . of course, derived biomass polymer is described "1st class biobased polymer" and bio-engineered polymer describe "2nd class biobased polymer".[2] Biodegradable polymers have possessed much interest due to their applications in biomedical and industrial fields, utilization of biodegradable polymers from regenerate sources can decrease environmental problems and together decrease the use of artificial polymers.[3] Biopolymers are assumed a many-sided substance, and their properties depend on the degree of interaction, molecular mass, and structure. The preparation of biopolymers with the required features is a complex and time-consuming process. To control this problem, the substitutional process is the biopolymer mixing technology but, this technique requires a particular notice about the mixture of biopolymers together and interactions.[4] The biopolymer-based delivery system is of importance because of their wide application areas, convenience, and nontoxicity.[5] Several industrial polymers are biologically inactive, though some showed toxicity, while others showed a wide area of therapeutic activities, several researchers have focused their interest on the production of a bioactive polymeric substance, by bounding the polymer to a drug through covalent bind, polymers are becoming more significant in pharmaceutical applications particularly in drugs delivery.[6] In recent years pains have directed to the preparation of reabsorbable, biodegradable, and biocompatible condensed polymers that can be applied in controlled drug release or to temporary industry implants, poly(glycolic acid), Poly(lactic acid) and their copolymer are used in clinical application.[7] The behavior of a polymeric drug in vivo commonly depends on the hydrolytic of a division of enzyme of the drug modify from the polymer; this allows the advantage of the sustained and delayed release of the drug over a long time with the reduction of side effects.[8]

Controlled drug delivery system (DDS) is one of the most favorable applications to human health interest and perform a develop field continuously for biomedical substances, the drug delivery system is described as the formula which controls the period and rate of drug delivery and target specific areas in the body, DDS is prepared to preserve therapeutic levels through the treatment period.[9] Polymeric drug delivery system is considered for several applications to complement the basic means of medical therapeutics. This drug delivery system is less complex and smaller than mechanistic pumps in order that the drug can be stocked as the dry powder in a polymer, new drug delivery system, which response to changes of the environmental conditions, e.g., pH, temperature, electric field, light (visible or ultraviolet) and confirmed chemicals are search.[10] Drug delivery systems are of great significance to regulation the rate of drug release in vivo and the concentration of optimal treatment.[11] Chitosan is a natural polymer and polysaccharide; it is partially deacetylated from

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chitin, which can be removed from crustacea. It is formation from N-acetylglucosamine and glucosamine units linked by 1–4 glycosidic bonds.[12] Chitosan is of commercial advantage because of their biodegradability, excellent biocompatibility, adsorption power, chelating, and non-toxicity. With these features, chitosan has several important applications in the pharmaceutical industry and biotechnology food, in environmental engineering, cosmetics, in aquaculture and agriculture.[13] Chitosan is used in the number of pharmaceutical and biomedical applications, including controlled or prolonged-release drug delivery system, blood anticoagulants and wound dressings . It is soluble in diluted organic and inorganic acids with pH lower than pKa of chitosan (about 6.3).[14] The reactive of the functional groups in chitosan are primary , secondary hydroxyl groups on C-2, C-3, C-6 positions and amino group. The amino groups in chitosan are the major factors that affect their physicochemical properties and structures and are interrelated with their flocculation, biological functions, and chelation.[15]

MEASUREMENTS

The intrinsic viscosity [η] measurements were carried out in water using an Ostwald Viscometer suspended level viscometer. The IR spectra measurements were recorded using a device Fourier Trans Infrared Spector Promoter –Shimadzu within range (500─3500). 1H NMR was taken at 300 MHz in DMSO. TMS was used as a reference.

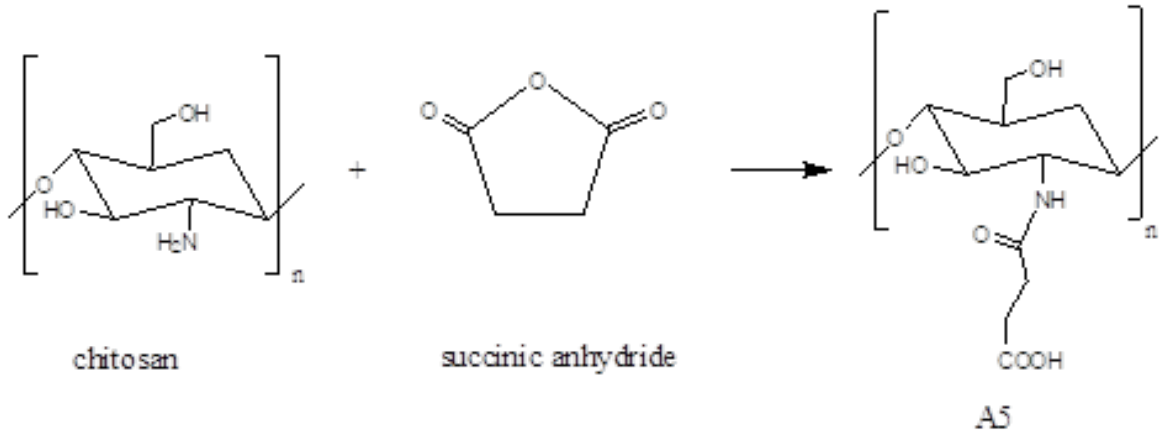
Experimental

The reaction of chitosan with succinic anhydride (A5)

1.5 g of chitosan (0.0103 moles) was dissolved in glacial acetic acid (0.1 N) and two drops of NaOH (0.01 N) 1.5 g of succinic anhydride (0.015 moles) was dissolved in dioxin then added to the solution of chitosan, the mixture was heated at 50 ˚C for half hour, the resulting was filtered and washed by diethyl ether for purification then the resulting was dried.

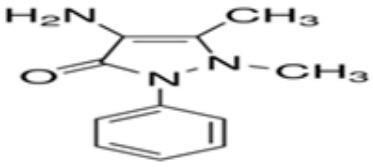
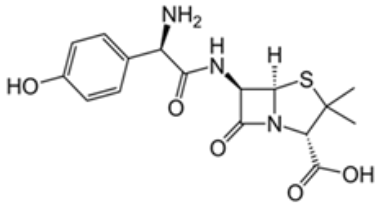
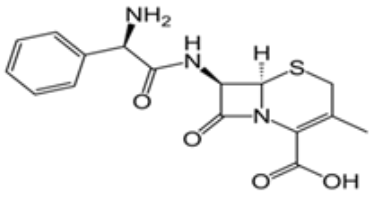
Preparation of polymers A8-A10

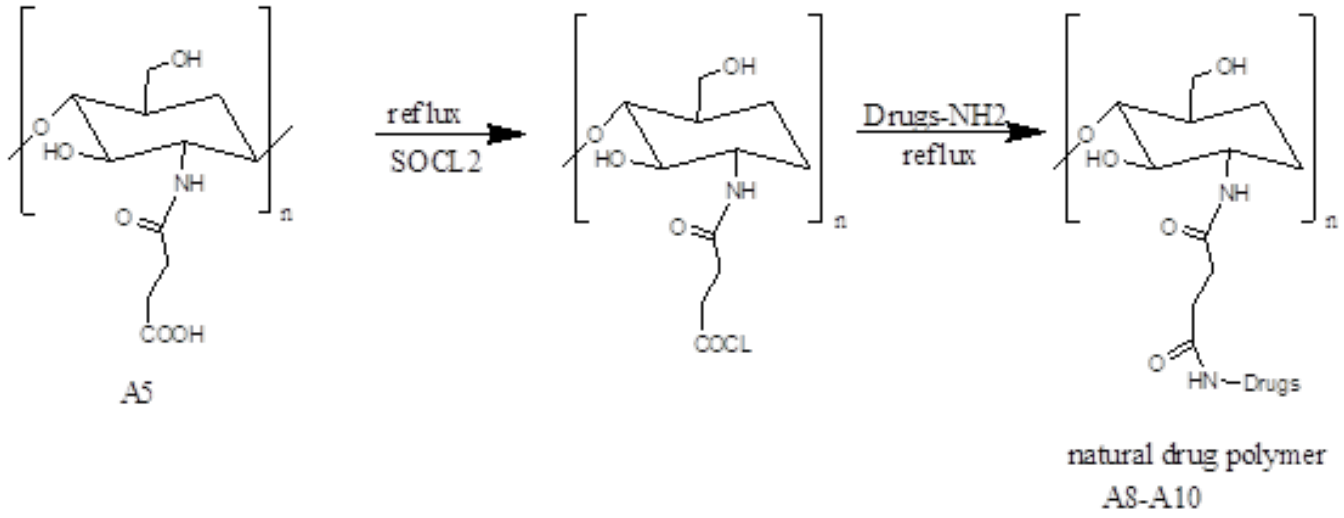
0.5 g of A5 was dissolved in water and heated, then two drops



Scheme 1: preparation of polymer A5

Table 1: Shows some of the physical properties of the compounds (A8-A10)

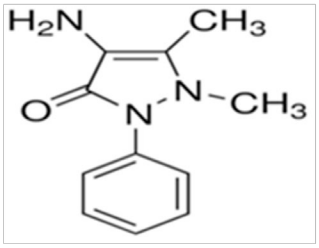
Sample	*Drug*	*Color*	*Yield %*	*Viscosity η=dl/g*	*Solvent*
A8		brouwn	68 %	0.72	Distilled water
A9		orange	29 %	0.86	Distilled water + heat
A10		Orange	50 %	0.6	DMSO + heat

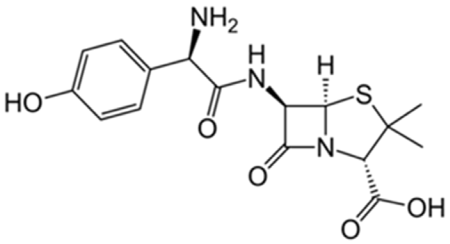


Scheme 2: preparation of polymers A8-A10

Drugs :

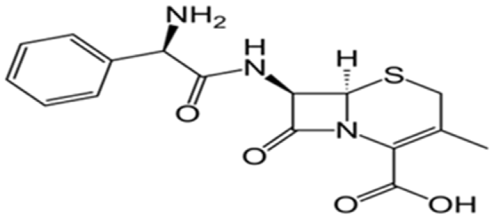
A8=4-amino antipyrine A9=amoxicillin A10=cephalexin





Cephalexin 4-aminoantipyrine

amoxicillin



of SOCL2 was added to the solution; the mixture was heated with constant stirring (magnetic stirrer) at 70 ˚C for a half-hour. An amount of 0.5 g of the amino drug (4-amino antipyrine) was dissolved in dioxan and DMF and added to the solution of A5. The mixture was heated at 70˚C for one and half hour, the result was filtered and washed by diethyl ether for purification then the resulting was dried, the experiment was reused with other amino drugs (amoxicillin, cephalexin), the biological activity of the following polymers was studied against positive and negative bacteria. And the viscosity of this polymers was measured using ostowalled viscometer . The following table shows the characteristics of the resulting compounds.

RESULTS AND DISCUSSION

Preparation and diagnosis of polymers A8-A10

Fourier-transform infrared spectroscopy (FT-IR) spectrum of A8 shows : 3528 (NH amide), 3415 (OH alcohol), 1654 (C=O amide), 3150 (=CH alkene), 3053 (=CH aromatic), 2915 (CH alkane), 1638(C=C alkene), 1603(C=C aromatic), 1068 (C-O-C ether). ^{1}HNMR spectrum shows 1.2 ppm for the proton of CH3, 2.4 ppm for the proton of CH2 (cyclic ring), 3.4 ppm for the proton of OH, 7.2 ppm for the proton of CH (aromatic), 7.5 ppm for the proton of NH (amide).

FT-IR spectrum of A9 shows: 3746 (NH amide), 3200 (OH alcohol),3300(OH phenol), 2400-3400(OH carboxylic

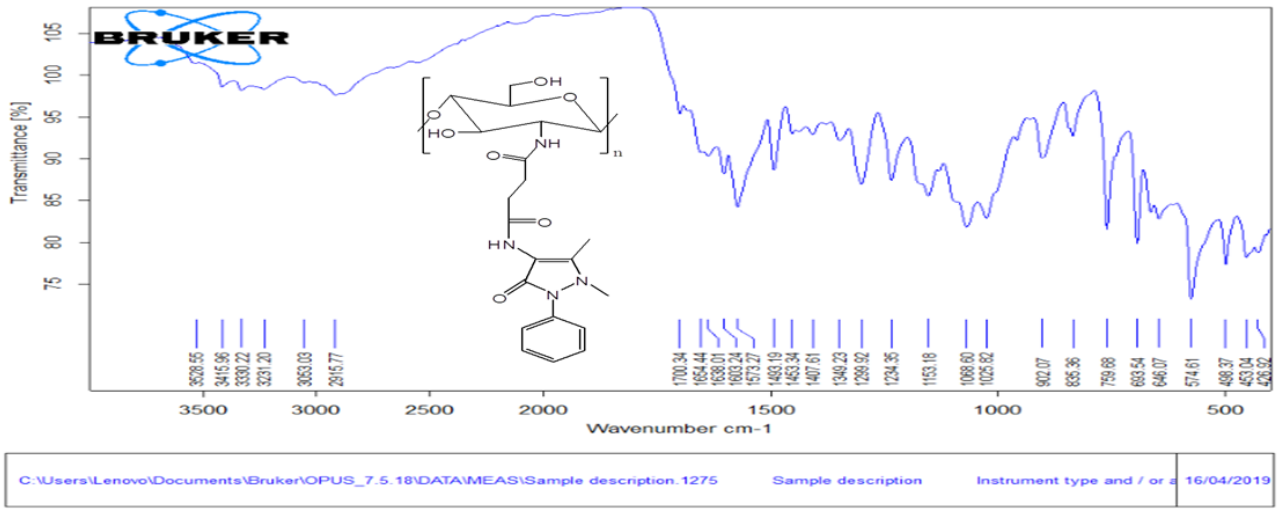


Figure 1: FT-IR spectrum of polymer A8

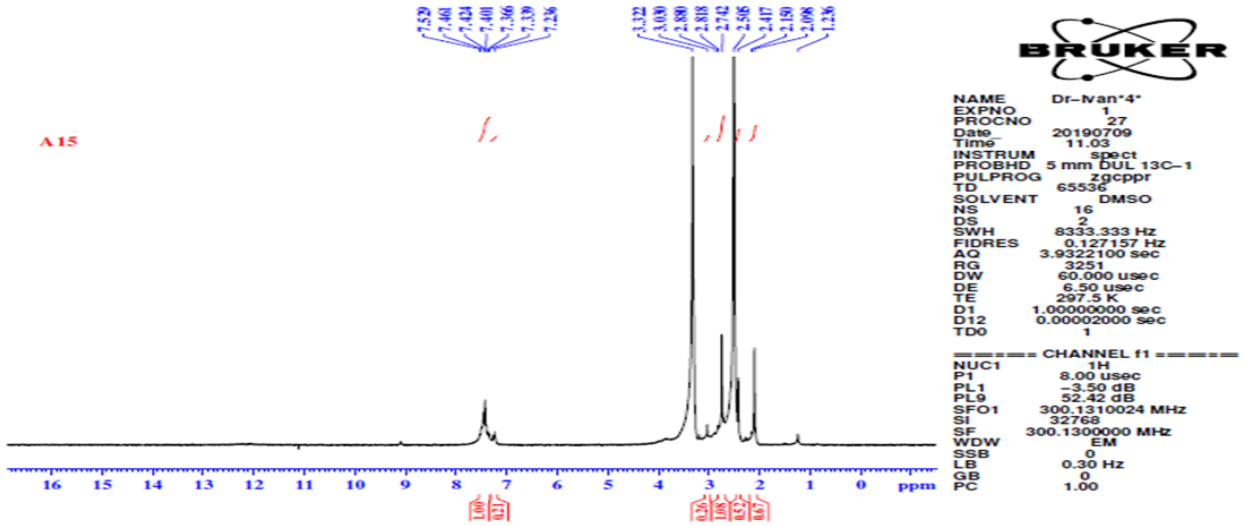


Figure 2: [1]HNMR spectrum of polymer A8

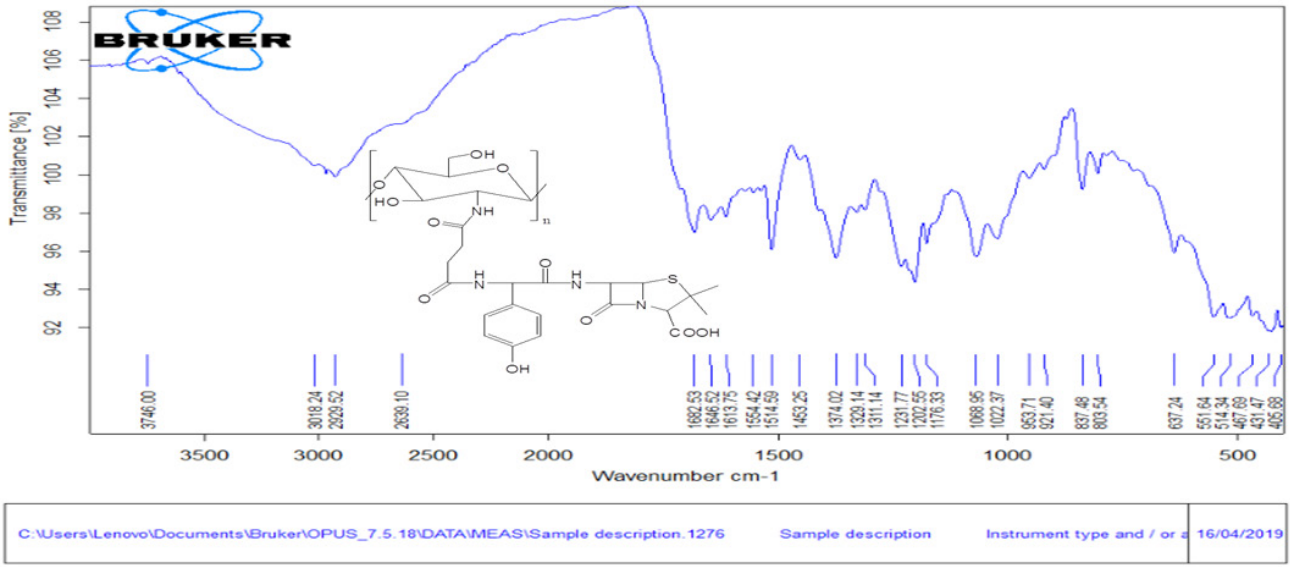


Figure 3: FT-IR spectrum of polymer A9

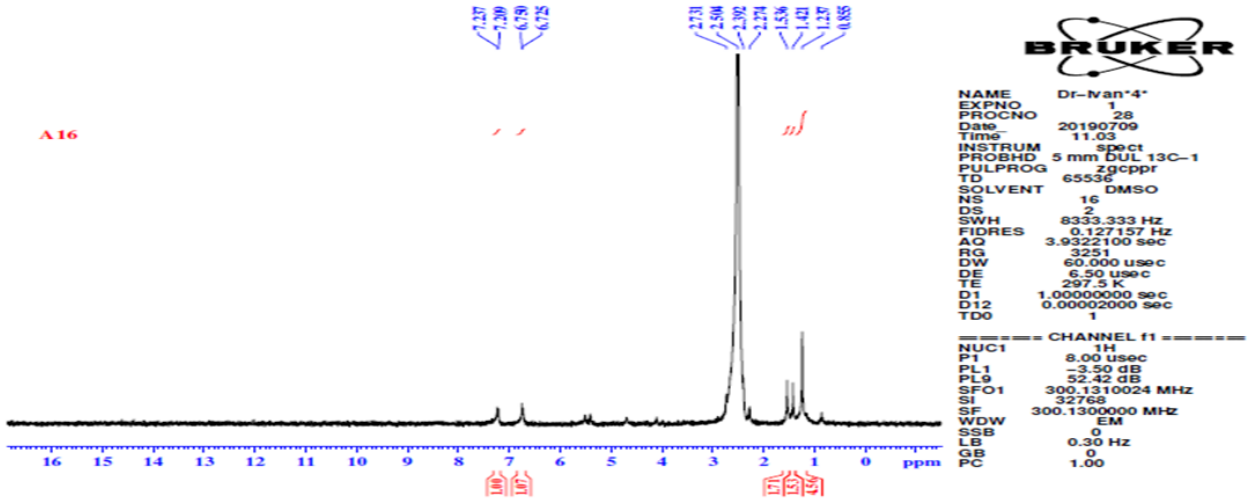


Figure 4: [1]HNMR spectrum of polymer A9

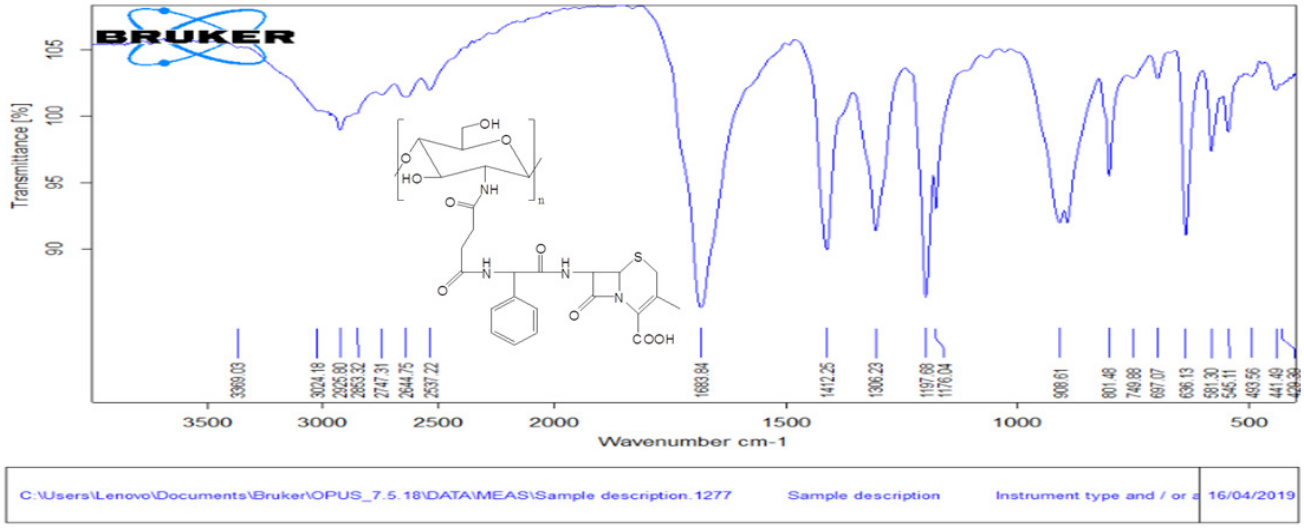


Figure 5: FT-IR spectrum of polymer A10

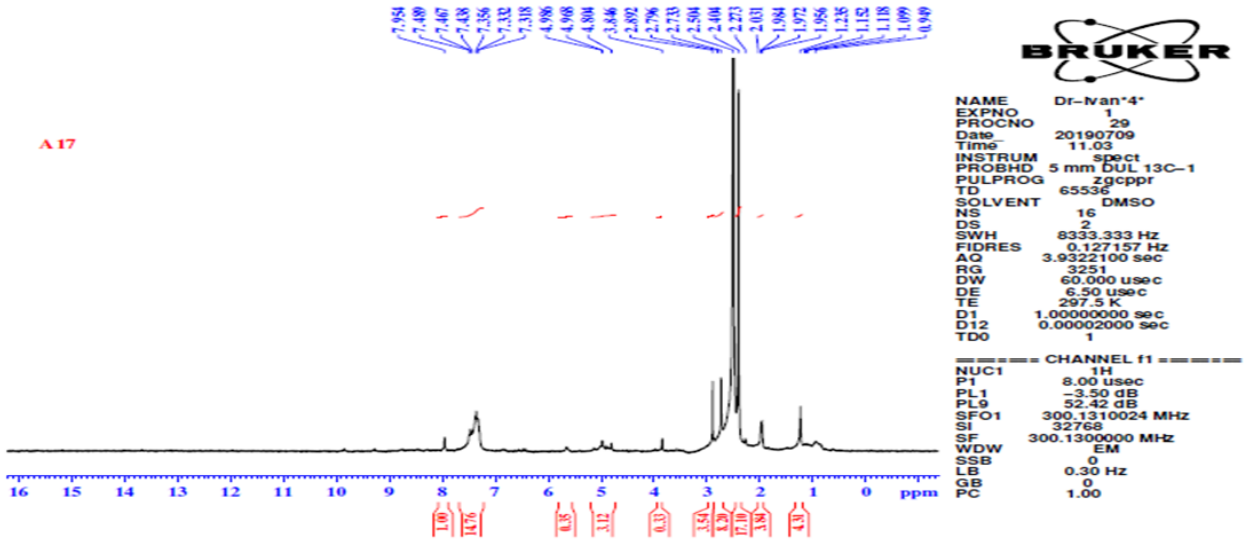


Figure 6: [1]HNMR spectrum of polymer A10

acid),1682(C=O carboxylic acid), 1646 (C=O amide),3018(=CH aromatic) 1613 (C=C aromatic), 2929 (CH alkane),2639 (SH mercaptan), 1068 (C-O-C ether), ^{1}HNMR spectrum shows: 1.2 ppm for proton of CH3, 1.5 ppm for proton of CH2 (cyclic ring), 4.1 -4.7 ppm for proton of OH, 6.7 ppm for proton of NH (amide), 7.3 ppm for proton of CH (aromatic).

FT-IR spectrum of A10 shows: 3369 (NH amide) , 3400 (OH alcohol) ,2400-3400 (OH carboxylic acid), 1683(C=O carboxylic acid),3024(=CH alkene) , 2925(=CH aromatic), 1500 (C=O amide), 1600 (C=C alkene), 1412 (C=C aromatic), 2853 (CH alkane),2537(SH mercaptan), 1197 (C-O-C ether), ^{1}HNMR spectrum shows: 0.9 ppm for proton of CH3, 2 ppm for proton of CH2 (cyclic ring), 3.8 ppm for proton of CH (between ring), 5.7 ppm for proton of OH, 6.5 – 7 ppm for proton of CH (aromatic), 8 ppm for proton of NH (amide), 9.3 – 9.8 ppm for proton of OH (carboxylic acid).

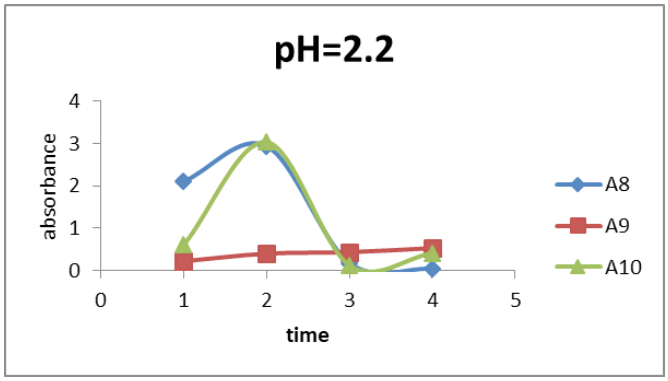


Figure 7 : drug release of polymers A8-A10 at pH = 2.2

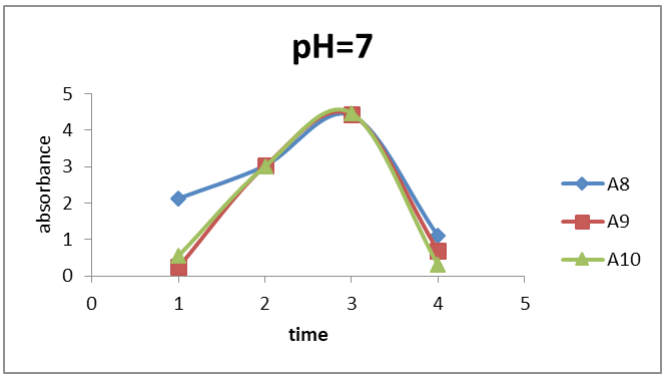


Figure 8: Drug release of polymers A8-A10 at pH = 7

Table 2: Drug release of polymers A8-A10 at pH = 2.2 at 37 ˚C

Time	*A8*	*A9*	*A10*
1	2.105	0.224	0.607
2	2.9393	0.4031	3.032
3	0.1816	0.4372	0.128
4	0.0447	0.5328	0.4142

Table 3: Drug release of polymers A8-A10 at pH = 7 at 37 ˚C

Time	*A8*	*A9*	*A10*
1	2.131	0.245	0.552
2	3.032	3.0236	3.015
3	4.4159	4.4378	4.481
4	1.098	0.6959	0.2965

Swelling ratio % and drug release

Drug release of the polymers A8-A10 was studied, Acid and base functions were used where hydrolysis was gradual. As a pharmaceutical unit of the hydrolysis of the polymer loaded with the drug where pH = 2.2, pH = 7 , pH = 8

It is also known that interlocking polymers have a solvent resistance because of the tangent that is specific to the chain movement, but the polymer is bulging due to the spread of solvent molecules in the polymer network within the crystalline network in the process of bloating in polymers with high molecular weight and volume change causing polymer collapse During the exposure the mechanical stress through the process of bloating is known as the degree of polymer bonding because the more the degree of entanglement occurs resistance to the

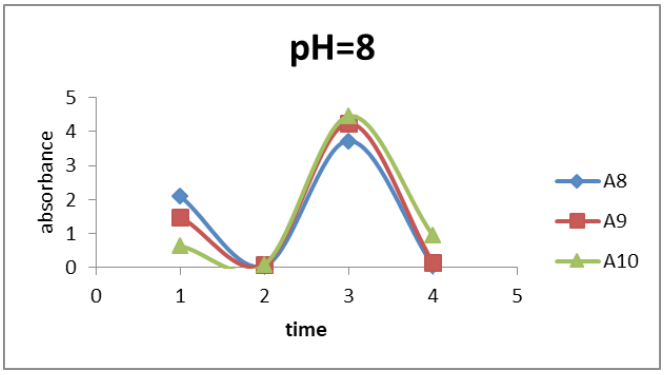


Figure 9: Drug release of polymers A8-A10 at pH = 8

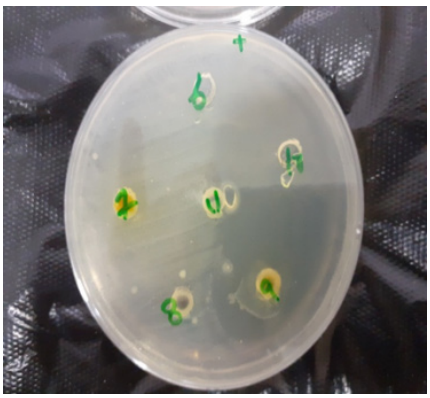


Figure 10: The biological activity of polymers A9

Table 4: drug release of polymers A8-A10 at pH = 8 at 37 ˚C

Time	*A8*	*A9*	*A10*
1	2.098	1.493	0.638
2	0.0559	0.106	0.0945
3	3.7305	4.2439	4.4541
4	0.0657	0.1595	0.95

Table 5: The swelling ratio % of polymers A8-A10

Sample	*Swelling ratio %*
A8	9
A9	15
A10	13

Table 6: shows the biological activity of polymer A9

sample	+	-
A9	30	10

bulge. The polymer and solvent molecules overlap in such a way that the polymer chain is not completely dissociated. polymeric layers are inflated due to polymer saturation with the appropriate solvent, but they do not dissolve

Biological activity

the biological activity of the polymer A9 was studied against positive bacteria (staphylococcus aureus) and negative bacteria (E.coli).

CONCLUSION

New drug polymers were prepared from the interaction of chitosan with succinic anhydride then interaction with amino drugs, All these polymers were characterized by FT-IR and ^{1}H-NMR spectrum and displayed characteristic bands proving the formation of the desired target molecules from the starting material. The physical properties of all prepared polymers were studied. The rapid release of prepared polymers was studied. Acid and base functions were used where hydrolysis gradually where PH = 2.2, PH = 7, and PH= 8 . most these polymers dissolve in water, Viscosity measurements in water were carried out using an Ostowalled viscometer, the biological activity of the following polymers was studied against positive and negative bacteria and found that the polymer A9 more biological activity against positive bacteria (staphylococcus aureus) and negative bacteria (E.coli) . The swelling of this polymers was measured using water for 24 hour at 25 ˚C, polymeric layers are inflated due to polymer saturation with the appropriate solvent, but they do not dissolve

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