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Research Article

Synthesis a novel nano co-polymer and using as carrier drug system

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ABSTRACT
In this work, a novel nano co-polymer was prepared from the reaction of phthalic anhydride with glycerol, as it was diagnosed by the infrared spectroscopy and the XRD technique. This nano co-polymer has been linked to five types of drugs (Amoxicillin, Cefalexine, Ampicillin, Mefenamic acid and Ciprofloxacine), and it was diagnosed by the infrared spectroscopy. The release of the drug from its binding to the nano co-polymer was performed, and it showed distinguished results in the release process in the basic medium (pH= 8.8).

Keywords: Amoxicillin, Cefalexine, Ampicillin, Mefenamic acid, Ciproflexase; Co- polymer; Nano co-polymer, carrier drug system, Swelling.

INTRODUCTION

The functional polymers used in medicinal applications have attracted a great attention, which includes several applications such as artificial organs, tissue engineering, medical devices, dentistry, etc. [1, 2]. The field of identification of polymers used as therapeutic agents and pharmacological properties for these polymers therefore can be useful as carriers for small molecules or macromolecules like proteins [3]. The synthetic polymers with biological materials can also be positive and eligible [4, 5]. Drug delivery systems are used for improving the therapeutic efficiency and safety of drugs by delivering them over the period of treatment to the site of action. Drug delivery systems may reduce the quantity and number of doses, biological inactivation and their side-effects [6]. Both non-degradable and biodegradable polymers used as pro-drug depends on two forms injectable and implants systems [7-10]. Carrier system which be consider ideal for used in intravascular systems is circulation of blood stream, blood-compatible, avoid excretion in kidneys and target area, desired rate and degrade in vivo during or after drug release [11-13]. Basically bioactive polymers have tremendous benefits due to their high molecular weight and their compatibility, therefore polymers appears to have many advantages over low molecular weight agents as therapeutic agents [14-16]. The advantages also include higher specificity of action, improved the activity due to their interactions and lower toxicity [17]. Some properties like issue of poly disparity in molecular weight and structural heterogeneity which make the development of process more complicated [18,19]. Higher molecular weight and potentially limited of pharmacological properties of polymers can be utilized to design and develop therapeutic agents for disease situations, while the drugs with low molecular weight have unsuccessful to produce therapeutic profiles [20].

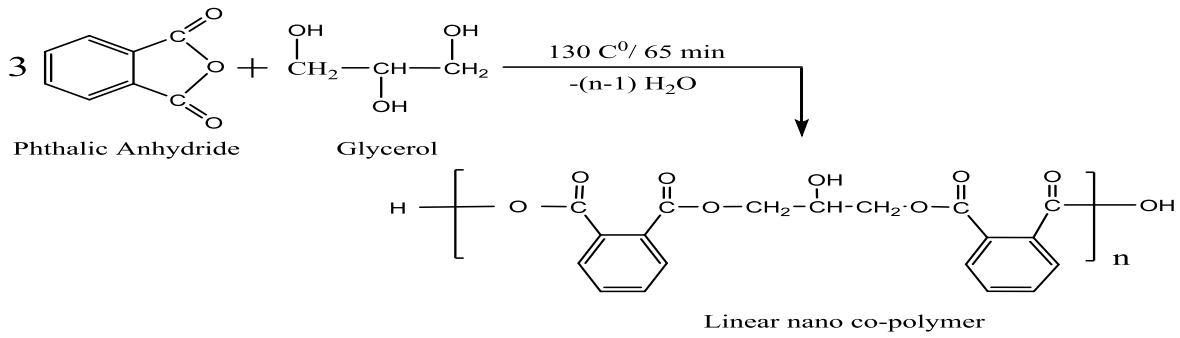
EXPERIMENTAL PART

Materials

A- All chemicals were used in this work analytical grade.
B- Preparation of three nano co-polymer.

Preparation of a linear nano co-polymer

In 200 ml beaker, (3.0 mole, 444gm) of phthalic anhydride and (70 ml) of DMSO, were mixed together. This flask was equipped with a thermometer. The mixture warmed carefully with a hot plate magnetic stirrer to70°C until clear liquor is formed and added (1.0 mole, 92gm) of glycerol to the solution. The mixture warmed carefully to 115°C then about 15 ml of xylene was added carefully to the reaction flask, in the form of batch (three drops in each batch), withdrawal of water formed by the esterification process, and the flask was gently heated. Heating was stopped after 65 min. at 130°C, until no more water came off to prepare linear nano co-polymer. Then add the cold distilled water, where the suspension solution is formed. Leave the suspension solution to precipitate overnight, then filtrated and wash with distilled water and leave to dry, as show in equation (1).



Equation (1): Synthesis of nano co-polymer

Figure (1) showed the FT-IR spectrum which appear a very weak broad band at (3093 cm^{-1}) attributed to the bond (O-H) alcoholic and H-bond, and showed a stretching band at (3067 cm^{-1} and 2887 cm^{-1}) attributed to the bond (C-H) aromatic and a asymmetric (C-H) aliphatic bond, also a strong stretching band at (1757 cm^{-1}) back to the ester bond (C=O), and showed a peak at (1107 cm^{-1}) attributed to the bond (C-O) ester, and shows bands at (709 and 903 cm^{-1}) attributed to di substitution of aromatic ring.

The size of particles of the nano co-polymer which prepared by using esterification process was measured by the atomic force microscope (AFM); The results showed that are nano particles co-polymer, as shown in the diagnosis as shown in figure (2 a, b & c) shows the outer surface of the nanoparticles of co-polymer. The roughness of this surface and the square root square are calculated according to the coefficient:

$$Rm \sqrt{\sum_{i=1}^{n} \frac{(Zi - Zav)^2}{N}}$$

Where N, Z = the number of measured points

The outer surface of the nanoparticles of co-polymer; the roughness coefficient of co-polymer surface was 5.08 nm and the square root square was equal to 5.94 nm.

This indicates that the bold size of the nanoparticles plays an important role in the roughness of the surface, its uniform crystalline system and the surface homogeneity. Also, the average of height of the particles was equal to 22.04 nm, as observed in figure (2 a). Table (1) represents the total rate of the particle sizes of the common nanoparticle and the different proportions of these volumes; the results indicate that the molecular size of the co-polymer nanoparticle was 68.62 nm and figure (3) represents the distribution of the different proportions of particle sizes of the co-polymer nanoparticle.

Figure (4) shows the x-ray diffraction (XRD) in the nanoparticles co-polymer using origin software. The average inters planer spacing between atoms (d_{hkl}) was 0.415 nm according to Bragg's Law:

$n\lambda = 2d\sin\theta$ ..... **Bragg's Law**

The total average crystallites size were 68.48 nm relative to Scherrer's equation:

$$D = \frac{k\lambda}{\beta\cos\theta}$$

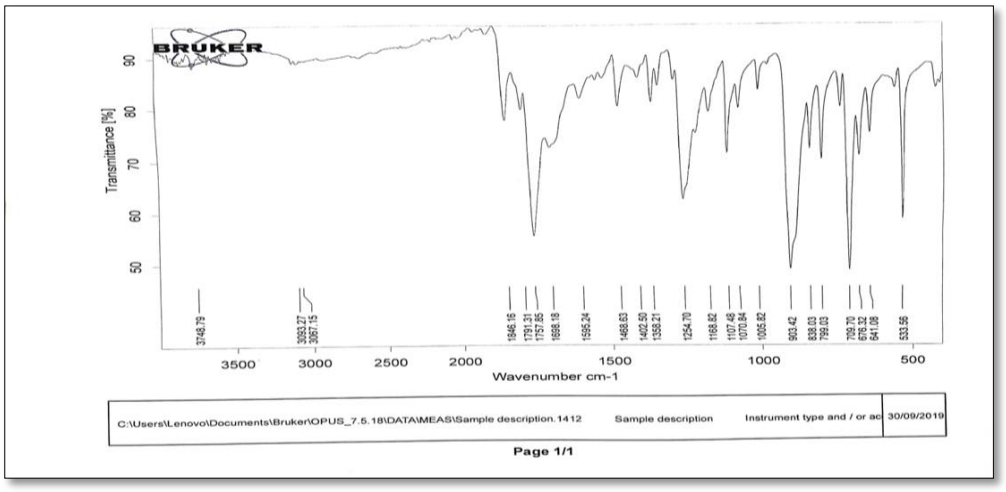


Fig.1: FT-IR spectrum of nano co-polymer

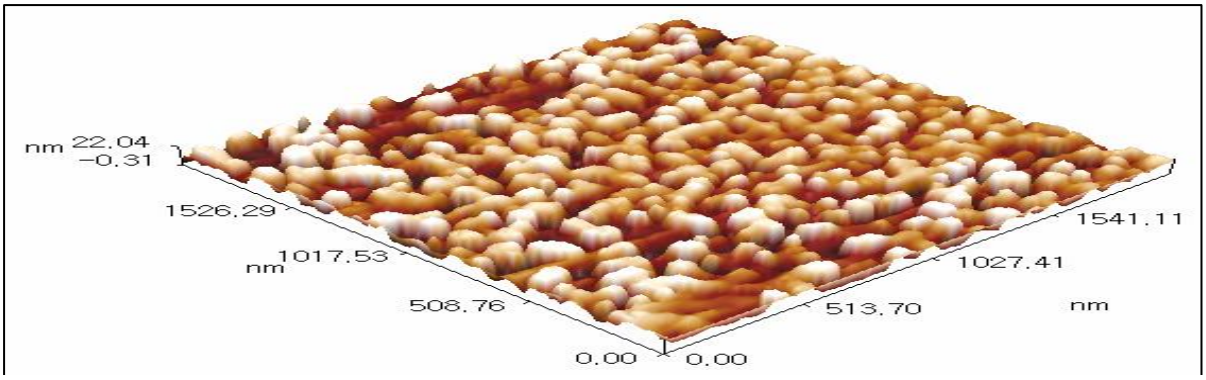


Fig.2(a): Image of Atomic Force Microscope for co-polymer shows 3D Image.

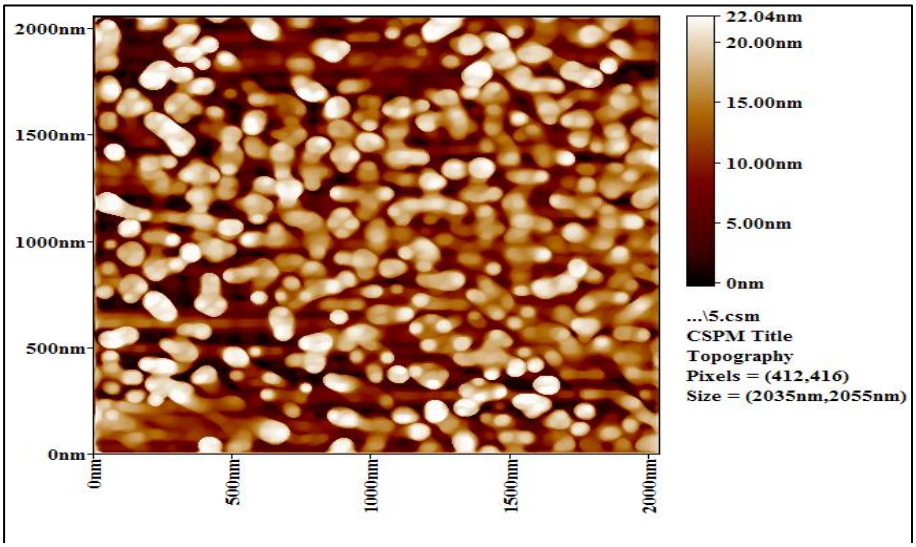


Figure 2(b): Image of Atomic Force Microscope for co-polymer shows 2D Image.

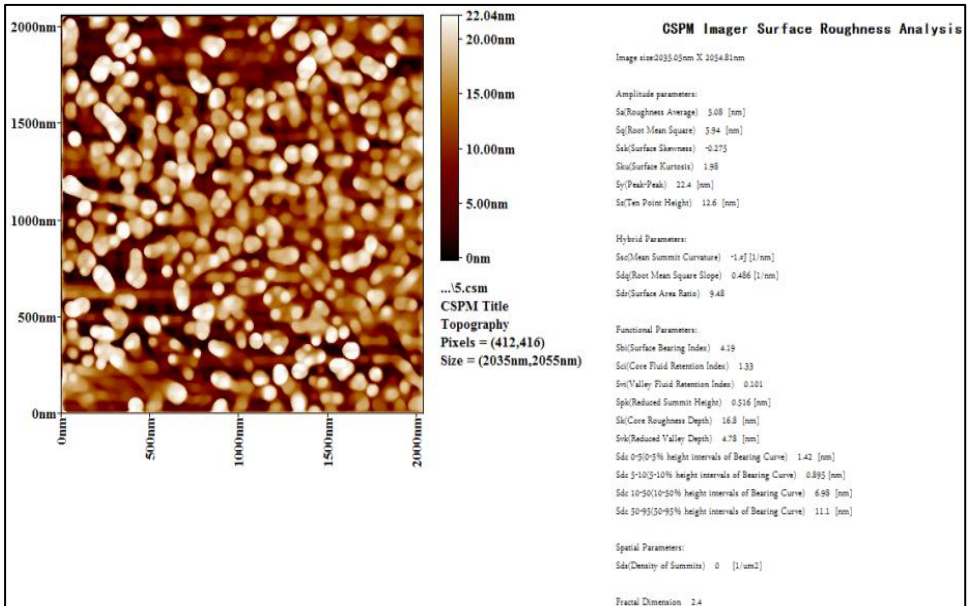


Fig.2(c): Image of Atomic Force Microscope for co-polymer shows 2D Image and showing all details of particles

Table 1: The total rate of the particle sizes of the nanoparticle co-polymer and the different proportions of these volumes

Sample: 1	**Code**: Sample Code
Line No.:lineno	**Grain No.**:264
Instrument: CSPM	**Date**: 2019-09-24
Avg. Diameter: 68.62 nm	**<=10% Diameter**: 50.00 nm
<=50% Diameter: 65.00 nm	**<=90% Diameter**: 80.00 nm

Diameter(nm)<	Volume (%)	Cumulation(%)	Diameter(nm)<	Volume (%)	Cumulation(%)	Diameter(nm)<	Volume (%)	Cumulation(%)
45.00	1.52	1.52	65.00	17.80	40.91	85.00	11.74	90.91
50.00	4.17	5.68	70.00	12.12	53.03	90.00	9.09	100.00
55.00	9.09	14.77	75.00	13.64	66.67			
60.00	8.33	23.11	80.00	12.50	79.17			

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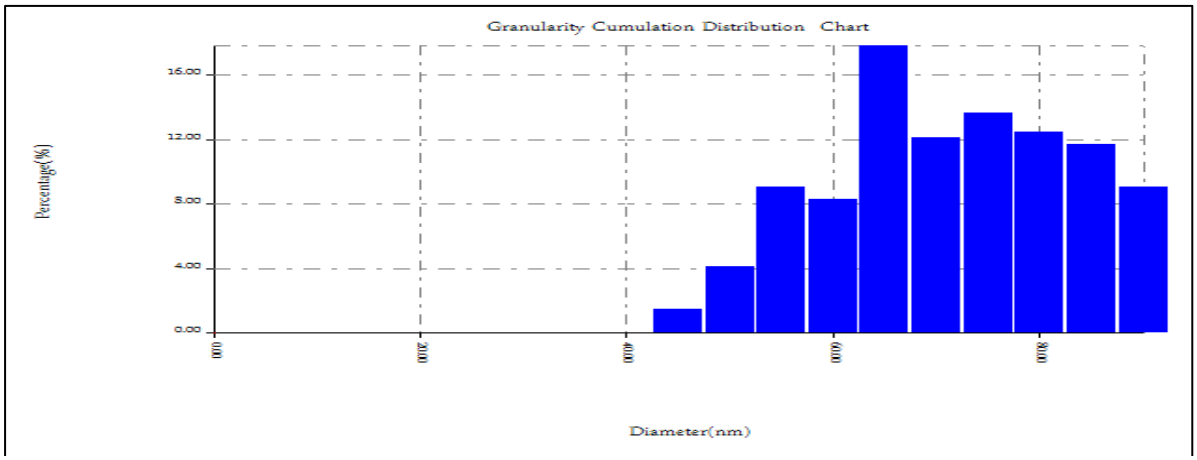


Fig.3: Distribution of the different proportions of particle sizes of the co-polymer nanoparticle.

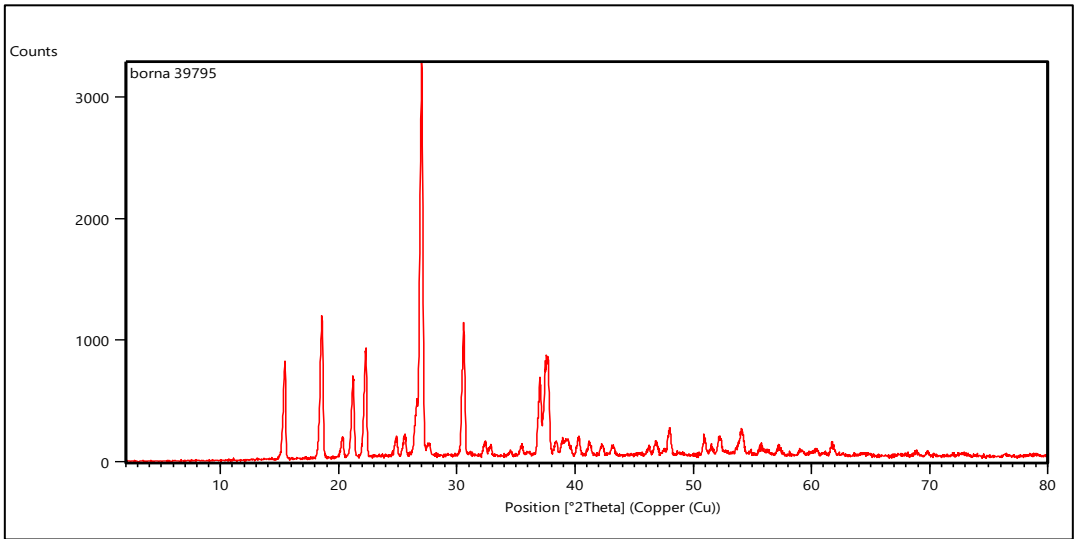


Fig.4: The x-ray diffraction in the nanoparticles co-polymer

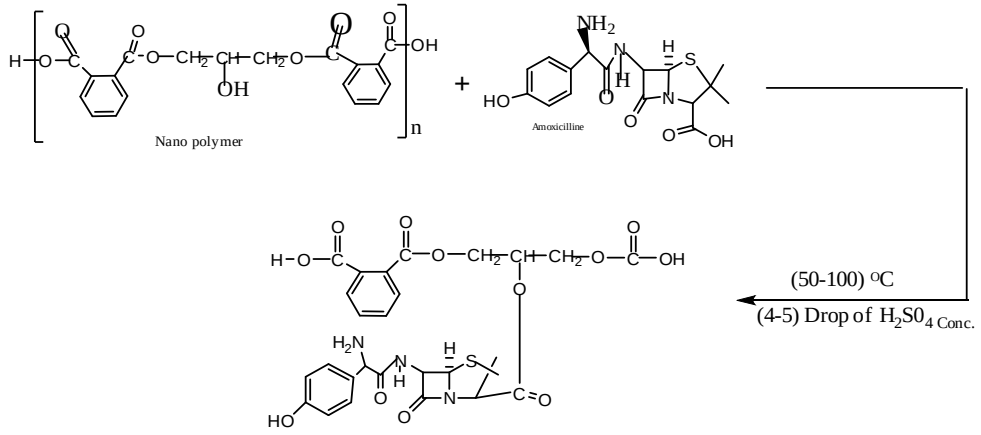
Table 2: The proportions crystallites sizes and the distances between atoms (d-spacing) in the nano co-polymer.

2 θ	θ	FWHM	D nm	d_{hkl} nm	D (Av.) nm	d_{hkl} (Av.) nm
15.41888	7.70944	0.103080717	77.77159	0.57421	68.4874	0.4152
18.56158	9.28079	0.121762332	66.10961	0.477637		
21.20363	10.601815	0.116152466	69.58317	0.418681		
22.26382	11.13191	0.117430493	68.94823	0.398978		
26.9992	13.4996	0.132757848	61.54072	0.32998		
30.55913	15.279565	0.12296861	66.97155	0.292302		

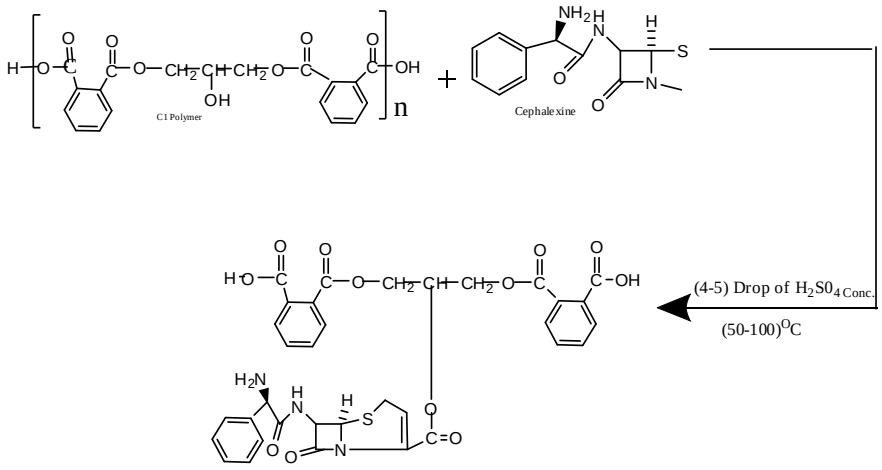
A general method of synthesis drugs with nano co-polymer

In (50ml) beaker, (0.5g) of nano co-polymer mixed with (0.5g) of Amoxicillin placed in the magnetic stirrer hot plate heater and raise temperature gradually starting than 50°C to 100°C with the addition of 4 to 5 drops of H_2SO4 Conc. Gradually with stirring continuous after melts mixture and leaves to cool and filter the mixture and washed by using acetone as a solvent, then leave to dry.

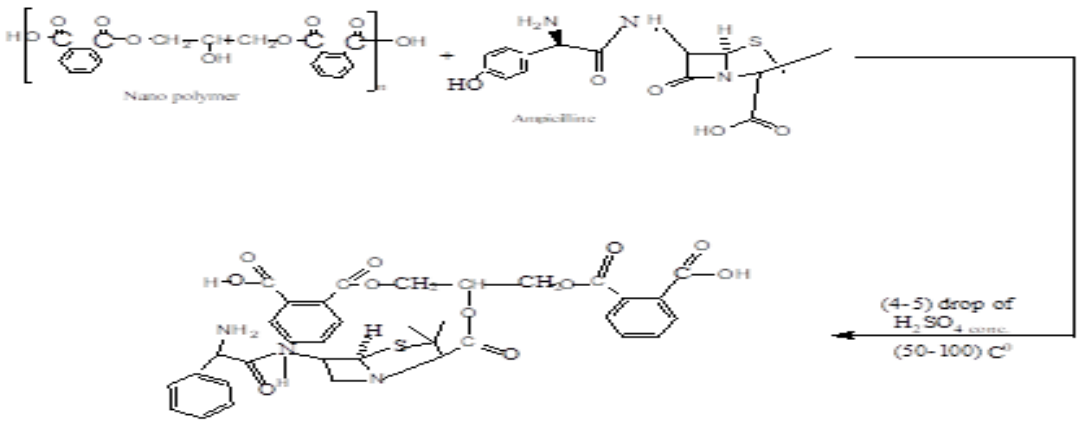
The same method above is used to prepare pharmaceutical compounds (Cefalexine, Ampicillin, Mefenamic acid and Ciprofloxacine) with the nano co-polymer. Equations (2 to 6) represent synthesis of drug compounds.



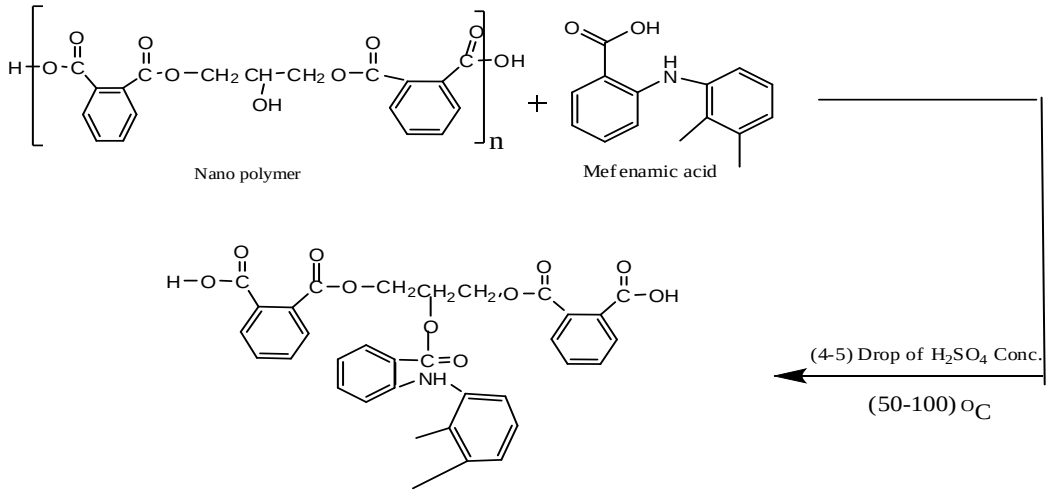
Equation (2): Synthesis of nano co-polymer with Amoxicillin



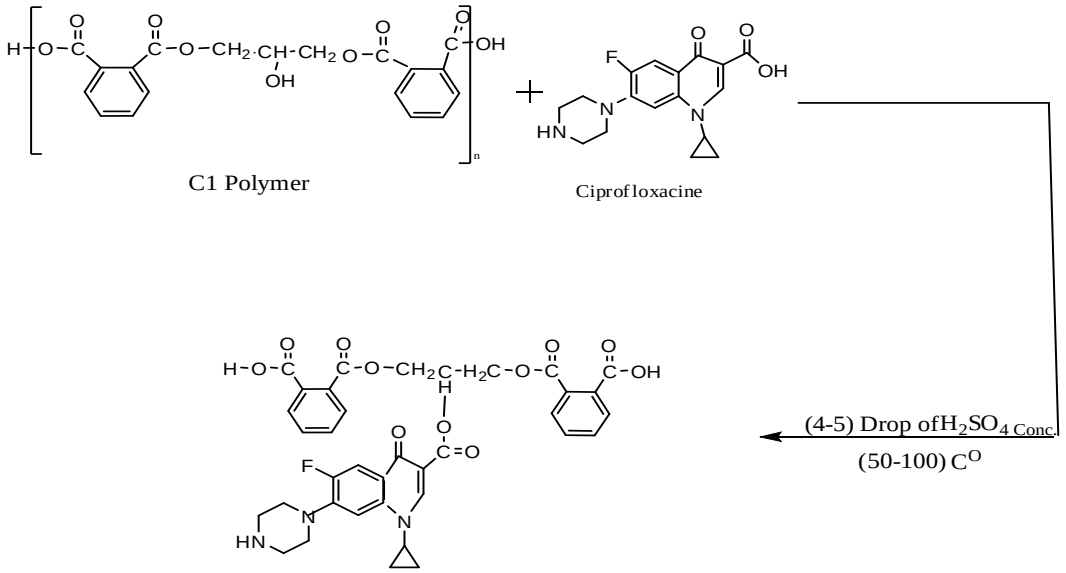
Equation (3): Synthesis of nano co-polymer with Cefalexine



Equation (4): Synthesis of nano co-polymer with Ampicillin



Equation (5): Synthesis of nano co-polymer with Mefenamic acid



Equation (6): Synthesis of nano co-polymer with Ciprofloxacine

Figure (5), FT-IR of nano co-polymer with Amoxicillin, it is appear a weak broad band at (3029 cm^{-1}) attributed to the bond (O-H) alcoholic and H-boned, also a stretching band at (3060 cm^{-1}) attributed to the bond (C-H) aromatic, and appear a strong stretching band at (1651 cm^{-1}) back to the bond (C=O) ester, and appear a peak at (1104 cm^{-1}) attributed to the

bond (C-O) ester, and appear bands at (714.66 cm^{-1}) attributed to di substitution of aromatic ring, and b appear and at (1718cm^{-1}) attributed to the bond (C=O) carboxylic acid .

Figure (6), FT-IR of nano co-polymer with Cefalexine, it is a appear weak broad band at (3004 cm^{-1}) attributed to the bond (O-H) alcoholic and H-bonded, also a appear stretching band at (3069 cm^{-1}) attributed to the bond (C-H) aromatic, and appear a strong stretching band at (1671 cm^{-1}) back to the bond (C=O) ester, and appear a peak at (1070cm^{-1}) attributed to the bond (C-O) ester, and appear bands at (736.49 cm^{-1}) attributed to di substitution of aromatic ring, and appear bands at (1738.44cm^{-1}) attributed to the bond (C=O) carboxylic acid

Figure (7), FT-IR of nano co-polymer with Ampicillin, it is appear a weak broad band at (3004cm^{-1}) attributed to the bond (O-H) alcoholic and H-bonded, also a appear stretching band at (3060 cm^{-1}) attributed to the bond (N-H) aromatic, and appear a strong stretching band at (1672 cm^{-1}) back to the bond (C=O) ester, and appear a peak at (1139cm^{-1}) attributed to the bond (C-O) ester) , and appear bands at (736 cm^{-1}) attributed to di substitution of aromatic ring, and shows bands at (1738cm^{-1}) attributed to the bond (C=O) carboxylic acid

Figure (8), FT-IR of nano co-polymer with Mefenamic acid, it is appear a weak broad band at (3343cm^{-1}) attributed to the bond (O-H) alcoholic and H-bonded, also a appear stretching band at (3009cm^{-1}) attributed to the bond (N-H) aromatic, and appear a strong stretching band at (1658 cm^{-1}) back to the bond (C=O) ester, and appear a peak at (1026 cm^{-1}) attributed to the bond (C-O) ester, and shows bands at (733 cm^{-1}) attributed to di substitution of aromatic ring, , and appear bands at (1737cm^{-1}) attributed to the bond (C=O) carboxylic acid.

Figure (9), FT-IR of nano co-polymer with Ciprofloxacine, it is appear a weak broad band at (3432cm^{-1}) attributed to the bond (O-H) alcoholic and H-bonded, also a appear stretching band at (3014cm^{-1}) attributed to the bond (N-H), and appear a strong stretching band at (1720cm^{-1}) back to the bond (C=O) ester, and appear a peak at (11626cm^{-1}) attributed to the bond (C-O) ester) , and shows bands at (745cm^{-1}) attributed to di substitution of aromatic ring, , shows bands at (1720 cm^{-1}) attributed to the bond (C=O) carboxylic acid and appear (1025 and 1272 cm^{-1}) the bond (C-O).

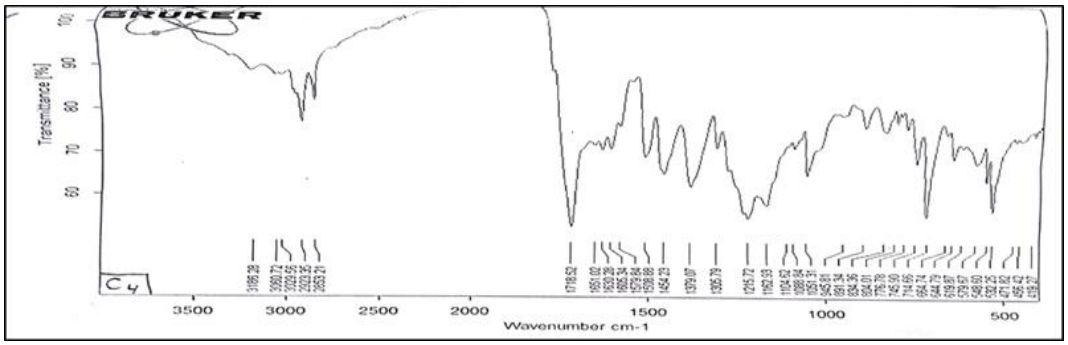


Fig.5:FT-IR of nano co-polymer with Amoxicillin

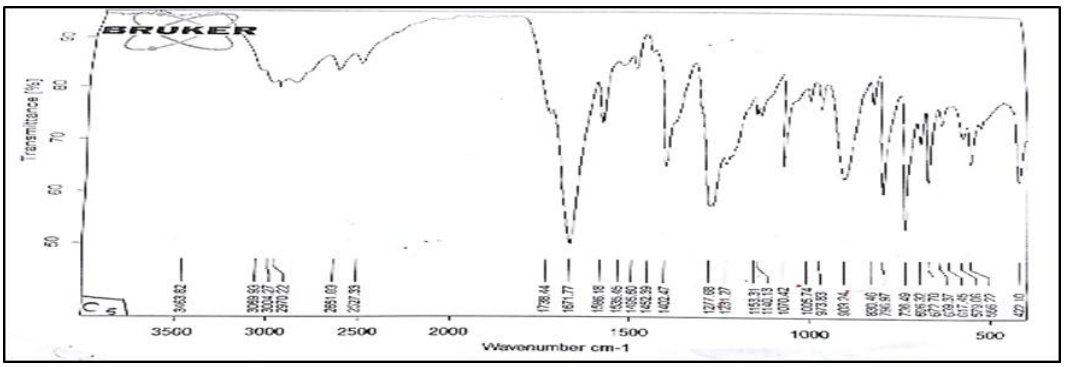


Fig.6: FT-IR of nano co-polymer with Cefalexine

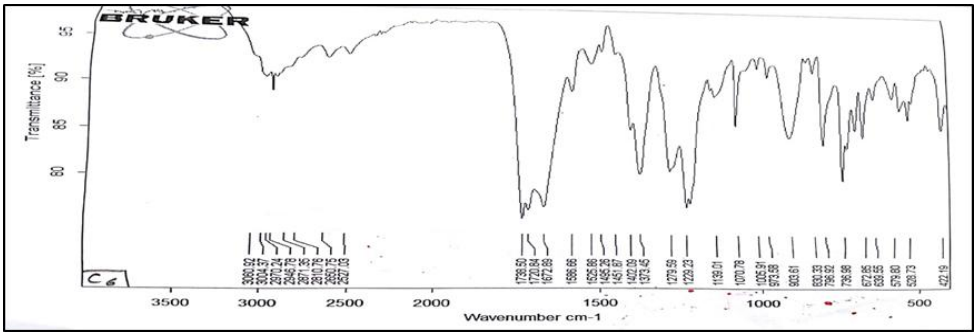


Fig.7:FT-IR of nano co-polymer with Ampicillin

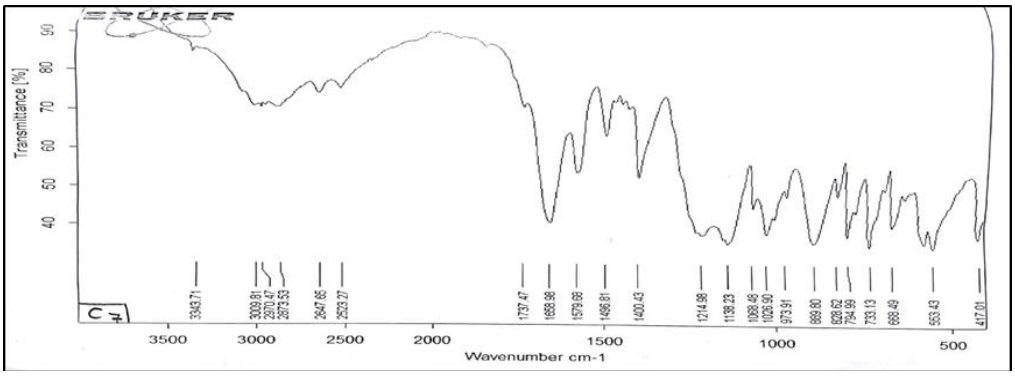


Fig.8:FT-IR of nano co-polymer with Mefenamic acid

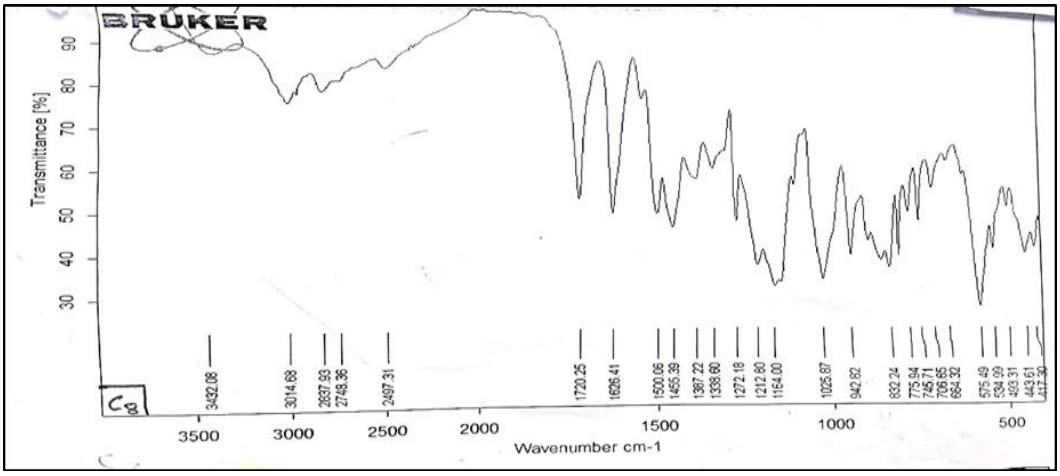


Fig.9:FT-IR of nano co-polymer with Ciprofloxacine

Release of drugs

By using UV-visible spectrophotometer, the release of drug from the synthesis polymers was determined in two different buffer solutions (pH 2.2 and 8.0) at constant temperature 310 K. By immersing xerogel (0.05 g) from polymers in 50 mL of different buffer solutions, it was allowed to soak for different inverted of time at constant temperature 310 K. The hydrogel was removed from the buffer solution at the stipulated time and measure the absorbance of buffer solution in order to determine the amount of drug release [25].

RESULT AND DISCUSSION

Release of Drug

Tables (3) and (4), represent the release of drugs from the measured samples in the basic medium pH=8.0 at different time (hour and day) and constant temperature. Tables (5) and (6), represent drug release from measured models in the acidic medium pH=2.2 at different time (hour and day) and constant temperature.

Table 3: Release of drugs from the measured samples with time (hour) in the basic medium pH=8.0 at constant temperature 310K

Time	Types of nano co-polymer				
	Amoxicillin	Cefalexine	Ampicillin	Mefenamic acid	Ciprofloxacine
(Hour)	Abs.	Abs.	Abs.	Abs.	Abs.
1	1	0.197	0.612	0.099	0.182
2	1.152	0.271	0.759	0.122	0.221
3	1.256	0.354	0.835	0.194	0.236
4	1.277	0.421	1.002	0.228	0.286
5	1.366	0.551	1.146	0.254	0.354
6	1.366	0.551	1.146	0.254	0.354

Table 4: Release of drugs from the measured samples with time (day) in the basic medium pH=8.0 at constant temperature 310K

Time	Types of nano co-polymer				
	Amoxicillin	Cefalexine	Ampicillin	Mefenamic acid	Ciprofloxacine
(Day)	Abs.	Abs.	Abs.	Abs.	Abs.
1	2.106	0.668	1.199	0.341	0.442
2	2.241	0.798	1.491	0.362	0.599
3	3	0.881	1.772	0.391	0.671
4	3.247	0.992	2.005	0.421	0.825
5	3.477	1.509	2.444	0.441	1
6	4.121	1.788	2.652	0.488	1.441
7	4.199	2.131	3.199	0.502	2
8	4.199	2.131	3.199	0.502	2

Table 5: Release of drugs from the measured samples with time (hour) in the basic medium pH=2.2 at constant temperature 310K

Time	Types of nano co-polymer				
	Amoxicillin	Cefalexine	Ampicillin	Mefenamic acid	Ciprofloxacine
(Hour)	Abs.	Abs.	Abs.	Abs.	Abs.
1	0.862	0.184	0.229	0.075	0.129
2	0.961	0.212	0.244	0.079	0.133
3	1.002	0.242	0.279	0.099	0.159
4	1.0331	0.279	0.305	0.099	0.169
5	1.223	0.321	0.359	0.099	0.189
6	1.223	0.321	0.359	0.099	0.189

Table 6: Release of drugs from the measured samples with time (day) in the basic medium pH=2.2 at constant temperature 310K

Time	Types of nano co-polymer				
	Amoxicillin	Cefalexine	Ampicillin	Mefenamic acid	Ciprofloxacine
(Day)	Abs.	Abs.	Abs.	Abs.	Abs.
1	1.349	0.403	0.549	0.121	0.243
2	1.396	0.549	0.699	0.134	0.284
3	1.596	0.748	0.856	0.146	0.362
4	1.862	0.868	0.967	0.146	0.499
5	2.226	1.131	1.219	0.146	0.562
6	2.421	1.152	1.254	0.146	0.661
7	2.555	1.442	1.556	0.146	0.791
8	2.555	1.442	1.556	0.146	0.791

CONCLUSION

The results obtained from this work showed a high effectiveness of the nanoparticle polymer in the process of drug delivery, where the release values of the drug for each type of drug used in this work showed that these values increased significantly in the basal medium more than in the acidic medium, and these Results are appreciated.

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