RESEARCH ARTICLE

Study of the Effective Range of Drug Level Using a Novel Nano Co-polymer-Mefenamic Acid

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ABSTRACT

In the present work, the work is divided into two parts, the first include synthesis a novel nano co-polymer by the esterification reaction between phthalic anhydride and glycerol, as it was characterized *via* fourier transform infrared (FTIR), proton nuclear magnetic resonance (^{1}HNMR), carbon-13 nuclear magnetic resonance (^{13}CNMR), atomic force microscopy (AFM) and transmission electron microscopy (TEM) techniques. The second parts, mefenamic acid drug reaction with novel nano co-polymer by esterification reaction which synthesis in first stage to produced novel nano co-polymer mefenamic acid drug. because the urgent need to retain the drug within the effective range for longer time, this driving us to look for a new optimization method for drug release; therefore, the study included, the study of drug release in two values of pH 7.5 and 5, where the choice of these two values depends on that the pH of the extracellular tumor is in the range of 6.5–7, while the endosome and lysosome are 4.5–5.5. The study gave great results, by linking the drug (mefenamic acid) with the nano co-polymer.

Keywords: Esterification reaction, Condensation Polymerization, Selectivity, Buffer solution, Swelling, Drug delivery system, Mefenamic acid.

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INTRODUCTION

Over the past years, nanoparticle (NP) formulation has been the subject of intense research, in which a suitable NP formula has been selected as a technique based on the physical and chemical properties of the drug, such as solubility and chemical stability. Different NP manufacturing methods enable modification of physical and chemical properties such as size, structure, morphology and surface texture, but also affect drug loading.[1]

This theory covers the art of fabricating NPs from preformed polymers, where traditional methods of NP preparation, such as auto-preparation and emulsification-based methods, are presented, and the new approach in NP technology, in which many tests have been carried out for the nature of the polymer, drugs, solvents, toxicity, purification and drug stability.[2] The polymer layer, is made from monomers, by combining a specific polymeric material with a relatively high loading of the therapeutic drug in a thermal process, such as co-extrusion of the therapeutic drug with the polymeric material, where the therapeutic drug is dispersed and incorporated into the polymer as small particles, preferably having the maximum cross-sectional dimension is 10 μm.[3]

Control systems seek to improve the efficacy of drug therapy, and this includes, reducing side effects, increasing therapeutic activity for a longer period and reducing the number of times the drug is administered during the treatment period such as repeated injections. This can achieve two types of drug release control, namely time and distribution.[4] The process of releasing a drug, it becomes available for distribution, elimination, absorption, and metabolism and eventually becomes ready for pharmacological action. Release is divided into: (1) direct release: the drug in this case is more effective. As for absorption, it occurs when the drug is allowed to dissolve without prolonging, delaying or absorbing the drug. (2) modified release. There are several modes of pharmaceutical modified release, including prolonged release, in which the prolonged therapeutic effect of the drug is achieved by continuous release over a period of time extended after the application of a single dose, and the benefit of these types is to reduce the number of times the drug is taken twice at least from him in the treatment of direct editing.[5,6]

Dissolution or biodegradability can be brought in the case of hydrogels approximately via hydrolytic, enzymatic, or

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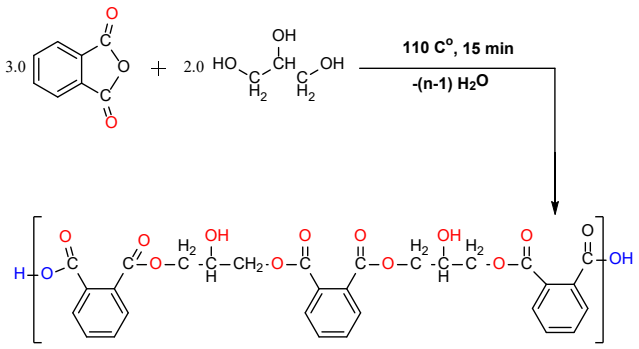


Equation 1: Synthesis of nano co-polymer

environmental (temperature, pH, or electric powered subject) pathways; but, the degradation isn't continuously ideal relying on the time frame and area of the drug transport tool.[7-10] Hydrogels, with excessive water content material in addition to tissue such as mechanical homes, and are showed being able to combine together with cells for engineer diverse tissues in each *in-vivo* and *in-vitro*.[11]

MATERIAL AND METHODS

All chemicals were used in this work of analytical grade.

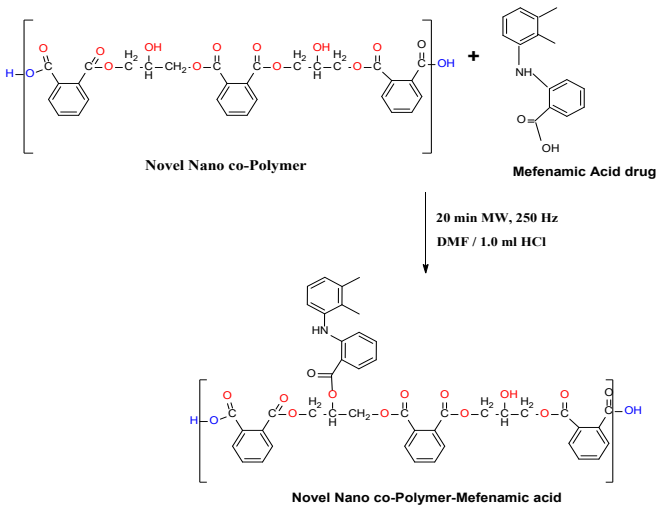
Synthesis of Novel Nano Co-polymer

The newly nano polymer namely (2,2'-((((phthaloylbis(oxy)) bis(2-hydroxypropane-3,1-diyl))bis(oxy))bis (carbonyl)) dibenzoic acid) by dissolving (444 gm, 3.0 mole) of phthalic anhydride in 250 mL round bottomed flask at (110°C) followed by addition of (184 gm, 2.0 mole) of glycerol. the reaction was continuously proceeding for 15 minutes escorting by batch addition of para-xylene if form of 3 drops every 5 minutes, in order to expulsion the water molecules that formed as a side product during the esterification reaction. Finally, deionized water was added to obtain suspension solution, and then the produced white precipitate was collected by filtration. Equation 1; this nano co-polymer was characterization by using fourier transform infrared (FTIR), proton nuclear magnetic resonance (^{1}HNMR), carbon-13 nuclear magnetic resonance (^{13}CNMR), atomic force microscopy (AFM) and transmission electron microscopy (TEM) techniques.

Synthesis of Novel Nano Co-polymer- Mefenamic Acid drug[12]

About (0.03 mmoL) of the nano co-polymer which contains carboxylic functional groups and two ratios of moles (0.03 and 0.06 mmoL) of mefenamic acid drug with 1.0 mL of concentrated HCl were mixed together in 30 mL pyrex vessel. Then introduced to a domestic microwave reactor and irradiated for 28 minutes with monitoring the reaction every 3 minutes. by TLC at 300 W. After that, 25 mL of diethyl ether was added, then the solution washed with (2.0 M) NaOH and leaved to dray overnight, as shown in Equation 2.

Release Drug from Novel Nano Co-polymer-Mefenamic Acid Drug[13]



Equation 2: Synthesis of Novel Nano Co-Polymer- Mefenamic Acid drug

The release of drug from the polymeric system in two pH values 5.0 and 7.5, by taking one gram of novel nano co-polymer- mefenamic acid drug and immersing it in a beaker containing 50 mL of buffer solution (pH=5.0 and pH=7.5), respectively, and the release is followed up every time (hour and day) by taking a sample of the solution and examining it with an UV-vis spectrophotometer.

RESULTS AND DISCUSSION

Synthesis of Nano Co-polymer

The physical properties of synthesis novel nano co-polymer were M.P. 240-242, yield 85%, color yellow and mobile phase was (ethanol 2.0: 0.75 hexane) and R*f* = 0.83. Figure 1, displays FTIR spectrum for a novel nano co-polymer; a broad band between 2400–3400 cm^{-1} for the stretching of the acidic OH group overlapped with the alcoholic OH group, 3057 cm^{-1} for the stretching vibration of sp^{2} aromatic (=CH) group, 2998 and 2873 returns to the stretching vibration of sp^{3} aliphatic (-CH) group, the band at 1760 cm^{-1} characterized to the esteric (C=O) linkage, 1667 cm^{-1} is the stretching vibration band of the (C=O) for terminal carboxylic groups, 1584 and 1470 cm^{-1} these two band returns to the aromatic (C=C). ^{1}H NMR (400 MHz,

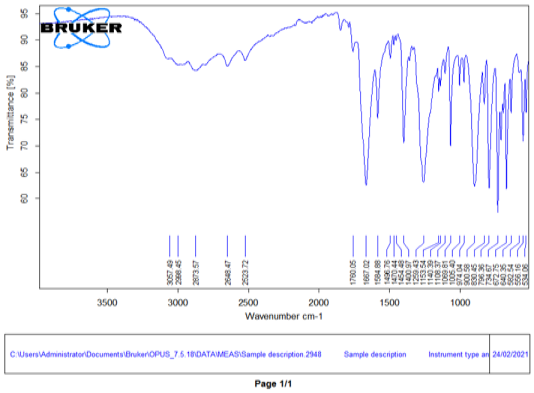


Figure 1: FT-IR spectrum of the synthesized novel nano co-polymer.

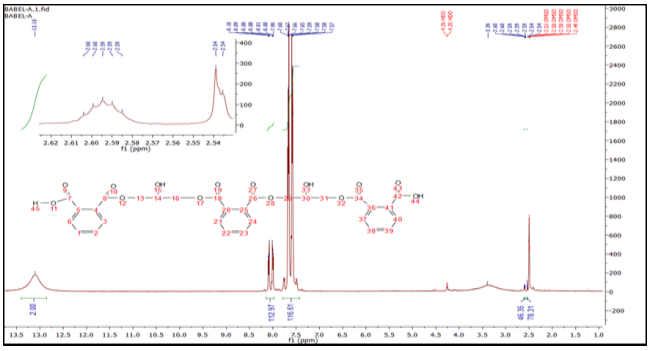


Figure 2: [1]HNMR spectrum of the synthesized novel nano co-polymer

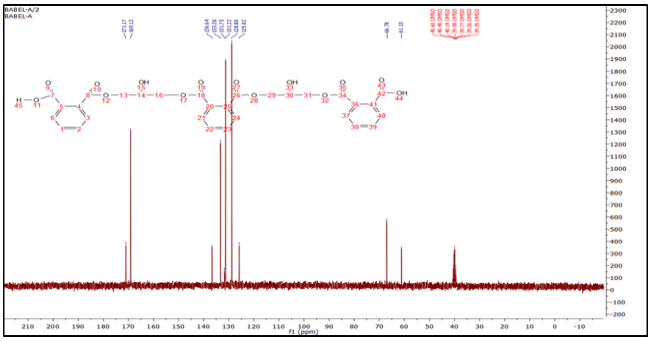


Figure 3: [13]CNMR spectrum of the synthesized novel nano co-polymer

DMSO-d6) δ; The singlet broad peak at 13.12 ppm assigned to the OH of the carboxylic groups, peaks from 8.09 to 7.97 are returns to the aromatic protons, peak at 7.4 and at 7.75 for the CH, as in Figures 2 and 3 show [13]CNMR (101 MHz, DMSO-d6) δ 169.12 (for the carbon of the carboxylic group 7 and 42), 167.2 (carbon 8, 34, 18 and 26), 136.8 (carbon 2 and 38), 136.6 (carbon 1, 4, 34 and 39), 133.28 (carbon 5, 20, 25 and 36), 131.73 (carbon 6 and 40), 131.22 (carbon 3, 21, 24 and 37), 85.3 (carbon 14 and 30), 82.6 (carbon 13, 16, 29 and 31).

The AFM technique was used as an initial indication that the synthesized co-polymer has a particle in the nano size range (10–100 nm). Figure 4 show the 1D and 2D AFM images for the outer surface of the synthesized co-polymer and Figure 5, show 1D micrograph and all other characteristics of the polymer surface. The roughness of the surface and the square of the root square were calculated as in Equation 3.

$$Rm\sqrt{\sum_{i=1}^{n}\frac{(Zi-Zav)^2}{N}} \quad \ldots\ldots\ldots 3$$

Where N, Z = the number of measured points.

The first evidence that the co-polymer is count as nano material is the roughness coefficient which equal to 29.3 nm, furthermore, its square root is 35.7 nm and this emphasize that the bulk size of the co-polymer nanoparticles has an importance in its roughness, in addition to its surface homogeneity and crystalline system. The AFM outcomes indicate the particles size of the polymer were 81.17 nm (Table 1).

Figure 6 displays the spectra of X-ray diffraction (XRD) for the co-polymer nanomaterial which refers that all the diffraction peaks appears in excellent matching with the previously synthesis nano co-polymer. The structure of the solid state for the synthesized co-polymer was tested by XRD

(A) **(B)**

Figure 4: (A) 1D and (B) 3D micrograph of the nano co-polymer surface.

Table 1: Outcomes of the AFM analysis for the synthesized nano co-polymer

Avg. Diameter: 81.17 nm				*<=10% Diameter:0 nm*				
<=50% Diameter:70.00 nm				*<=90% Diameter:100.00 nm*				
Diameter (nm)<	*Volume (%)*	*Cumulation (%)*	*Diameter (nm)<*	*Volume (%)*	*Cumulation (%)*	*Diameter (nm)<*	*Volume (%)*	*Cumulation (%)*
65.00	15.10	15.10	100.00	3.67	88.57	145.00	0.82	95.51
70.00	22.45	37.55	105.00	2.86	91.43	150.00	0.82	96.33
75.00	17.96	55.51	110.00	0.41	91.84	155.00	0.82	97.14
80.00	10.20	65.71	115.00	0.41	92.24	160.00	0.41	97.55
85.00	7.76	73.47	125.00	1.22	93.47	165.00	0.41	97.96
90.00	6.53	80.00	130.00	0.82	94.29	170.00	0.82	98.78
95.00	4.90	84.90	135.00	0.41	94.69	175.00	1.22	100.00

Table 2: TEM outcomes for the newly synthesized polymer

Label	*Area*	*Angle*	*Length*
1		-51.953	83.73
2		-153.027	100.536
3		-20.225	80.531
4		118.301	74.247
5		33.944	68.145
6		34.778	70.127
7		-144.904	72.355
8		37.093	82.241
9	Mean	-18.249	80.747
10	SD	94.56	91.923
11	Min	-153.027	95.73
12	Max	118.301	81.536

Table 3: Release of drug (Mefenamic Acid) per time (hours and days) in pH=5.0 and constant temp. 310k

Time (Hours)	*Mefenamic Acid drug Concentration*				
	Absorbance (λmax.)				
	0.2	*0.4*	*0.6*	*0.8*	*1.0*
1	0.162	0.174	0.188	0.198	0.215
2	0.196	0.213	0.223	0.234	0.261
3	0.232	0.258	0.264	0.279	0.295
4	0.278	0.288	0.301	0.319	0.341
(Days)					
1	0.305	0.335	0.373	0.413	0.465
2	0.354	0.384	0.455	0.478	0.535
3	0.435	0.462	0.512	0.566	0.586
4	0.482	0.506	0.534	0.586	0.618
5	0.482	0.506	0.534	0.586	0.618

Table 4: Release of drug (Mefenamic Acid) per time (hours and days) in pH=7.5 and constant temp. 310k

Time (Hours)	*Mefenamic Acid drug Concentration*				
	Absorbance (λmax.)				
	0.2	*0.4*	*0.6*	*0.8*	*1.0*
1	0.011	0.016	0.019	0.023	0.027
2	0.023	0.028	0.035	0.042	0.047
3	0.032	0.038	0.043	0.052	0.059
4	0.036	0.043	0.049	0.058	0.064
(Days)					
1	0.066	0.073	0.079	0.088	0.094
2	0.076	0.083	0.092	0.099	0.104
3	0.084	0.092	0.098	0.106	0.112
4	0.089	0.096	0.106	0.112	0.123
5	0.089	0.096	0.106	0.112	0.123

in order to determine its properties like purity, crystalline size and crystalline phase. When the size of the synthesized crystals is very small, a diffraction peaks must be appearing, so the appearance of this diffraction peaks is the graph of the studied

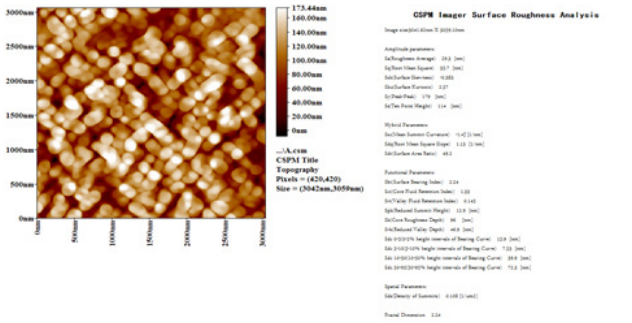


Figure 5: 1D micrograph and all other characteristics of the polymer surface.

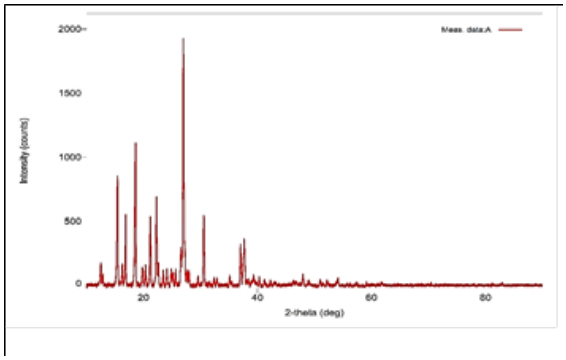


Figure 6: X-Ray spectrograph of the nano co-polymer.

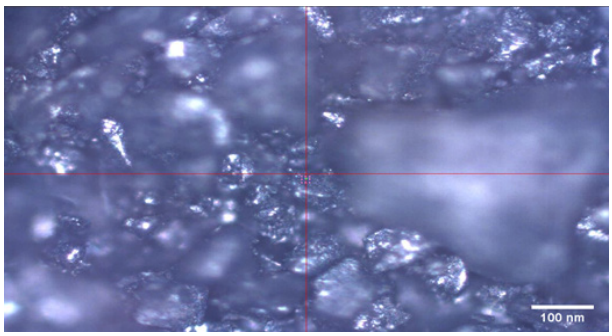


Figure 7: TEM image for the nano co-polymer particles.

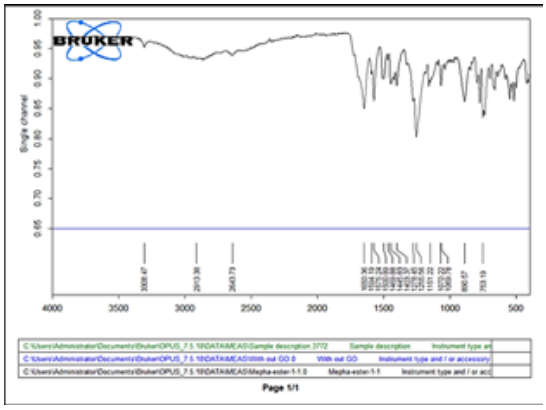


Figure 8: FT-IR spectrum of novel nano co-polymer- Mefenamic acid drug.

co-polymer refers to formation of this nano polymer, it has been reported that the decreasing in the crystal size is accompanied

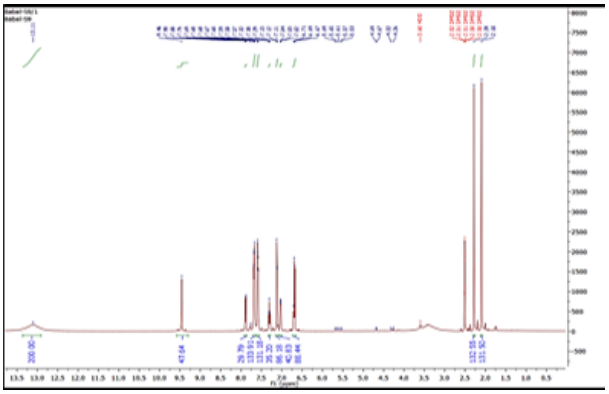


Figure 9: [1]HNMR spectrum of novel nano co-polymer- Mefenamic acid drug.

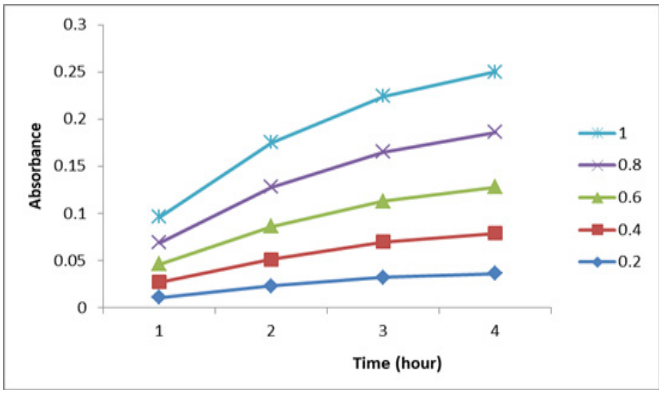


Figure 12: Release of drug per time (hour) in pH=7.5 at cons. temp. 310k.

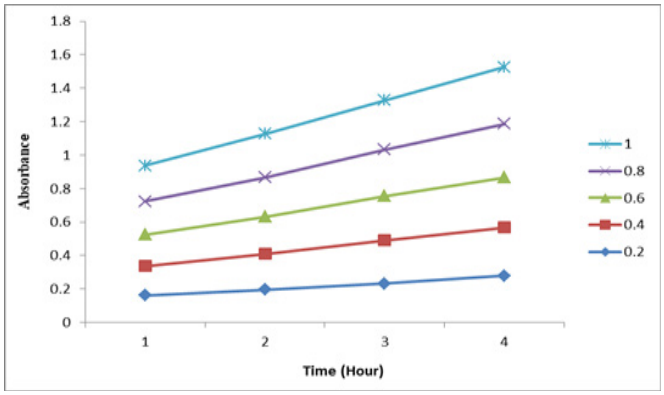


Figure 10: Release of drug per time (hours) in pH=5.0 at cons.temp. 310k.

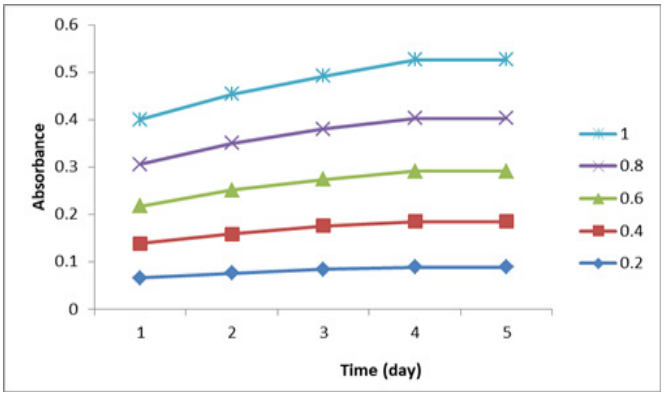


Figure 13: Release of drug per time (days) in pH=7.5 at cons. temp. 310k.

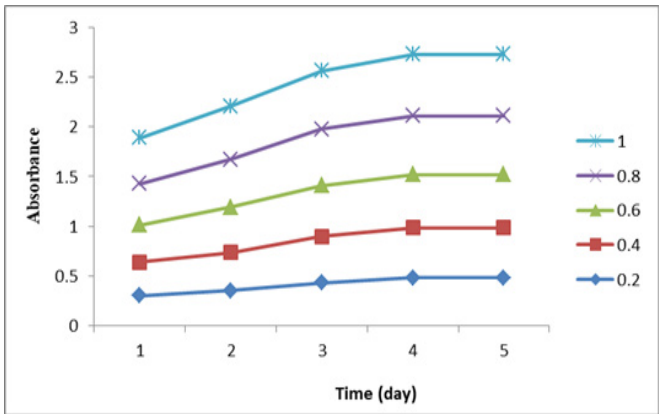


Figure 11: Release of drug per time (days) in pH=5.0 at cons. temp. 310k.

by increase in the intensity of these peaks. The space area of the XRD peaks attributed to four reasons: micro strain for instance lattice deformation, crystalline fracture which causes by defects of crystallization field size and the crystal domain size. The Debye-Scherer equation 4 was utilized to calculate the particle size for the copolymer nanomaterials:

$$D = \frac{k\,\lambda}{\beta \cos\theta} \quad \ldots\ldots\ldots\ldots\ldots (4)$$

Where: D and k represents the average of crystals size and shape factor respectively which is equal to 0.9, λ is the wave length of the X-ray radiation (0.1056 nm), β is the full width of half maximum height FWHM, finally θ is the deviation angle. This equation used to the average size of the polymer particles which is around (nm).

TEM technique used to accomplish more details about the particles structure of the surface, shape, distribution and size of the particles. The strength of the TEM magnification prove that the particles are nano sized and has a smooth surface and its shape like sheets as in Figure 7. It appeared that the nano particles of co-polymer have a diameter of (81.536) and length in range of (81.536–95.73) as in Table 2.

Synthesis of Novel Nano Co-polymer- Mefenamic Acid Drug

The physical properties of synthesis novel nano co-polymer were M.P. 325-327, yield 77%, color white-brown and mobile phase was (Ethanol 3 : 1 Hexane) and R*f* = 0.78. Figure 8, show the FTIR (KBr, cm^{-1}): ν 2500-3400 (OH), 2973 and 2859 (CH, sp3), 3307 (NH), 3012 (CH, sp^2 of aromatic rings), 1501 bend (NH), 1470 (bend of CH2), 1401(bend of CH3), 1647 (polymeric ester, C=O), 1594 (polymeric carboxyl, C=O).

Figure 9, showed ^{1}H NMR (400 MHz, DMSO-d6) δ broad singlet peak at 12.32 ppm for the polymeric hydroxyl group, singlet at 8.68 ppm for the drug free primary amine, singlet at 8.27 ppm for the NH of the secondary drug amide, 7.74–7.38 ppm for the protons of the polymeric aromatic benzene, 6.30

and 6.26 ppm for the protons of aromatic drug benzene, The multiplate peaks at 5.58–5.50 ppm to the proton of carbon 14 and 30, 5.19 ppm for the protons of atom 13 and 29, singlet at 4.86 ppm for the protons of atoms 16 and 31, 4.61 ppm for the proton of atom 52 and 75, 3.06 ppm for the proton of 61 and 84, 1.41 ppm for the protons of methyl groups.

Release Drug from Novel Nano Co-polymer-Mefenamic Acid drug

Tables 3, 4 and Figures 10, 11 are outlining the release of drug from the polymeric system in two pH values 5.0 and 7.5.

The choice of these two acidity values based on, that the pH of tumor extracellular is in the range of 6.5-7, whereas the endosome and lysosome are 4.5-5.5 (Figures 12, 13).

From the foregoing, it becomes clear to us that with the increase in the concentration of the released drug, the absorbance increases, and the greatest percentage of absorbance was in the acidity function pH=5.0 (Table 2, 3).

CONCLUSION

The phenomena that lead to transition the drug from its polymeric carrier into its desired site termed as “drug release”. When medication is abused, its levels in the human plasma are usually oscillated, in which at the beginning its level is too high then being decreases with time. So, the urgent need to retain the drug within the effective range for longer time, this driving as to look for a new optimization method for drug release. The choice of these two acidity values based on, that the pH of tumor extracellular is in the range of 6.5–7, whereas the endosome and lysosome are 4.5–5.5.

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