Study of the Effective Range of Drug Level Using a Nano Chitosan-Mefenamic Acid

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Abstract

In the present work, the work is divided into two parts, the first include synthesis a nano Chitosan-Mefenamic acid drug, by the esterification reaction between Chitosan and Mefenamic acid drug, as it was characterized via FT-IR, ^{1}HNMR, ^{13}CNMR and AFM techniques. The second parts; The study included, the study of drug release in two values (5.0 and 7.5) at constant temperature 310 K; where the choice of these two values depends on that the pH of the extracellular tumor is in the range of 6.5-7.5, while the endosome and lysosome are 4.5-5.5. The study gave great results, by linking the drug (Mefenamic acid) with the chitosan; 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.

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

1. 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 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 vivo and vitro (11).

2. Material And Methods

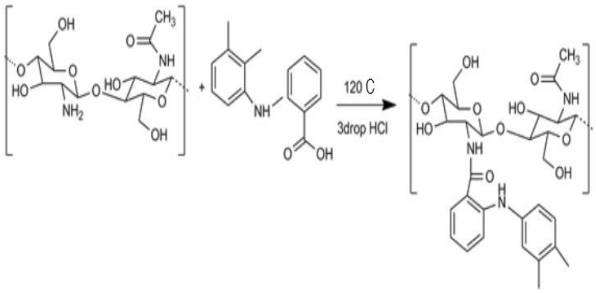
All chemicals were used in this work of analytical grade.

Synthesis of Nano Chitosan-Mefenamic Acid Drug

Mefenamic acid drug (7.5g, 0.03 moles) were dissolved in 30 ml THF with three drops of concentration HCl and added to nano chitosan (5.0g,

doi.org/10.31838/hiv23.02.45 Received: 13.10.22, Revised: 14.11.22, Accepted: 18.12.22

0.0005 moles) and reflex for 24 hr. Finally, the precipitate was washed by diethyl ether and 2.0 M NaOH and leave to dry for 16 hr. as in Equation 1.



Equation 1: Synthesis of nano Chitosan-Mefenamic acid drug

Release Drug from Nano Chitosan-Mefenamic acid drug

Using UV. -Vis. Spectrophotometer, release the Mefenamic acid drug from the synthesis nano chitosan- Mefenamic acid drug were determined in two different buffer solutions (5.0 and 7.5) at constant temperature 310 K.

3. Results and Discussion

Synthesis of Nano Chitosan-Mefenamic Acid Drug

The FT-IR spectrum of drug compound, Figure (1), shows appearance absorption band at 3182 cm^{-1} indicative of the presence of bond (O-H) alcoholic with H-bonded, and absorption band at 3419 cm^{-1}, on the presence of NH_2 and absorption band at 3080cm^{-1} indicative of aromatic C-H and absorption band at 2976 cm^{-1} indicative of the presence of aliphatic C-H, and absorption band at 1726 cm^{-1} indicative of the presence of C=O amide and absorption band at 1604 cm^{-1} indicating the presence of NH bend and also showed absorption band at 1263 cm^{-1} indicating the presence of C-O group.

Figure (2) shows the ^{1}HNMR spectrum, where appearance signal at 12.99 ppm for OH and appear signal at 9.44 ppm for the secondary drug amine and appearance signal at 7.89 ppm for the primary amine and appear signal at 7.32-6.67 ppm for the aromatic hydrogen and appearance signal at 5.1 ppm for the methylene group number 14 and appear signal at 3.83 ppm for methylene group number 6 and 11 and appear signal at 3.71 ppm for methylene group number 31 and 32.

The ^{13}CNMR spectrum for drug compound, Figure (3), where a signal appeared at 170.69 ppm for the C=O ester and a signal appeared at 149 ppm for the aromatic carbon drug number 19, 20 and 21 and a signal appeared at 150.02 ppm for the aromatic carbon drug number 29,31 and 30 and a signal appeared at 122.12 ppm for the aromatic carbon drug number 28, 27, 26 and 25 and a signal appeared at 126 ppm for the aromatic carbon drug number 18 and 23 and a signal appeared at 130.12 ppm for the aromatic carbon drug number 22 and a signal appeared for C-O of carbon number 5 at 40 ppm, and a signal appeared for the carbon drug number 31 and 32 at 20.39 ppm, and a signal appeared for the carbon number 14 at 14 ppm, and a signal of C-NH_2 appeared at 40.06 ppm.

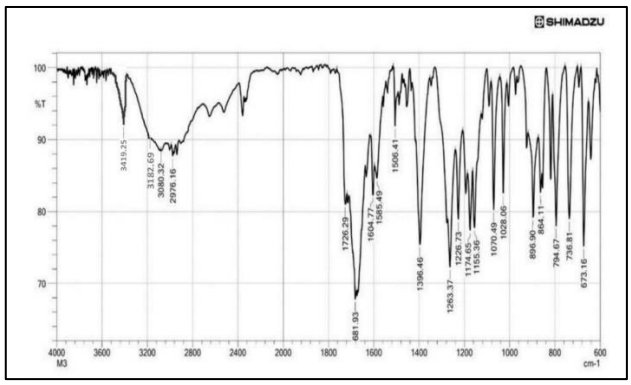


Figure (1): FT-IR spectrum of nano Chitosan- Mefenamic acid drug

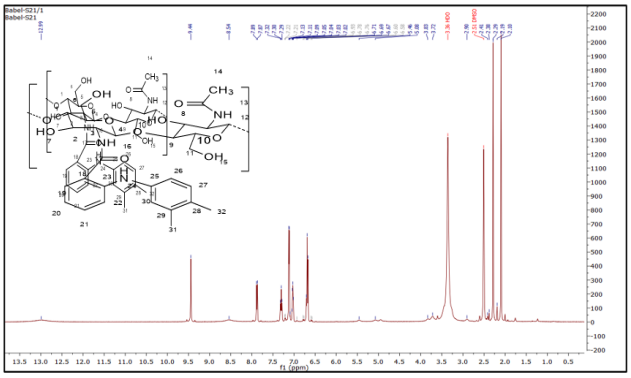


Figure (2): ^{1}H-NMR spectrum of nano Chitosan-Mefenamic acid drug

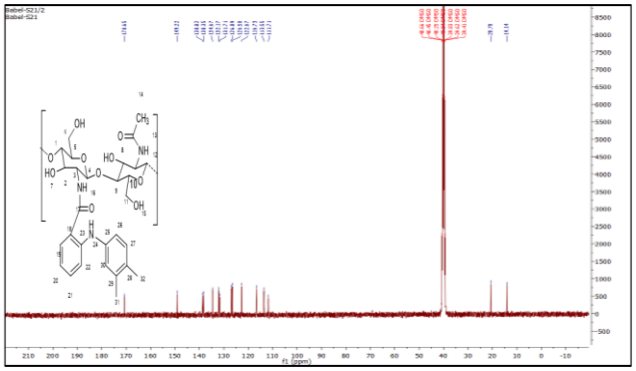


Figure (3): 13C-HNMR spectrum of nano Chitosan-Mefenamic acid drug

The AFM technique of nano Chitosan was used as an initial indication that the synthesized of nano Chitosan-Mefenamic acid drug 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 the Equation below:

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

Where N, Z = the number of measured points.

The first evidence that the nano Chitosan is account 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 nano Chitosan 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 nano Chitosan were 72.36 nm. as in Table 1.

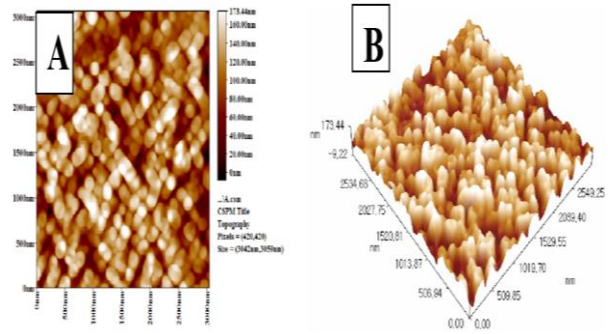


Figure (4): A) 1D and B) 3D micrograph of the nano Chitosan surface

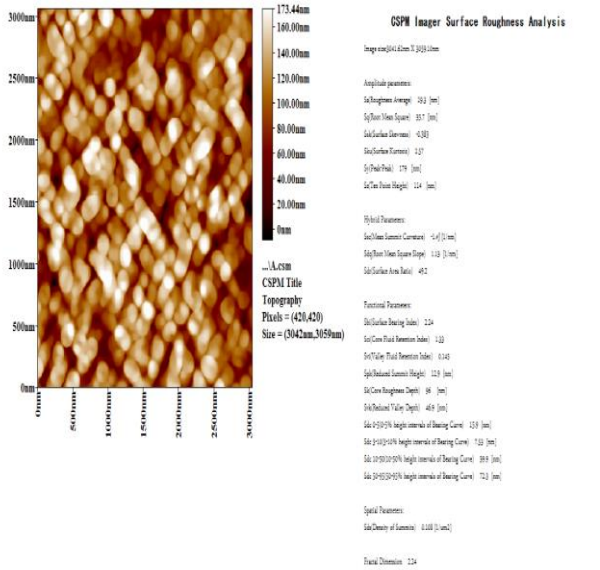


Figure (5): 1D micrograph and all other characteristics of nano Chitosan surface

Table (1): Outcomes of the AFM analysis for the synthesized nano Chitosan								
Avg. Diameter: 72.36 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

Release Drug from Nano Chitosan-Mefenamic acid drug

Tables (2, 3) and Figures (6) to (9) 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.

Table (2): 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 (λ max.)				
	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 (3): 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 (λ max.)				
	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

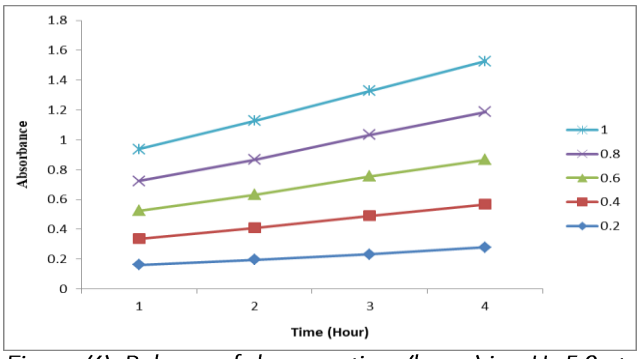


Figure (6): Release of drug per time (hours) in pH=5.0 at cons.temp. 310k

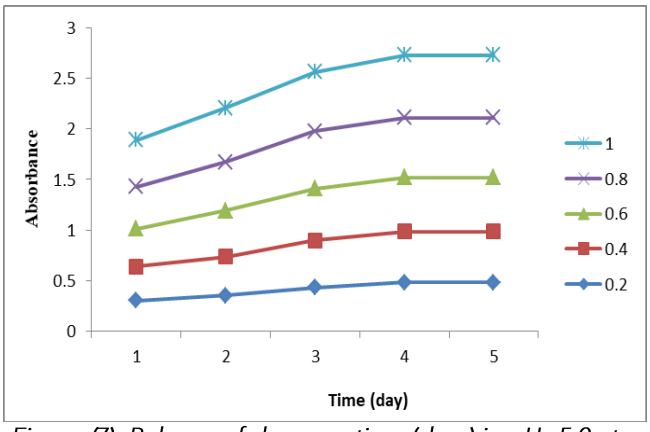


Figure (7): Release of drug per time (days) in pH=5.0 at cons. temp. 310k

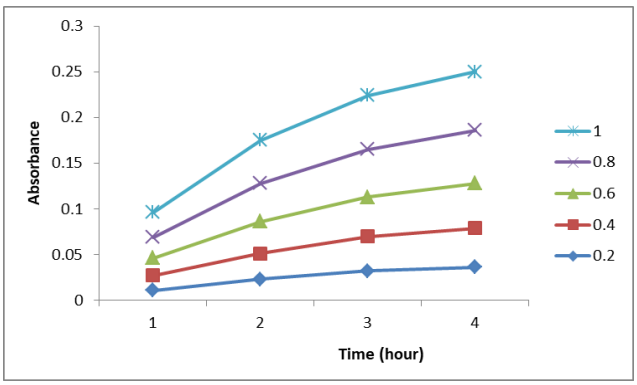


Figure (8): Release of drug per time (hour) in pH=7.5 at cons. temp. 310k

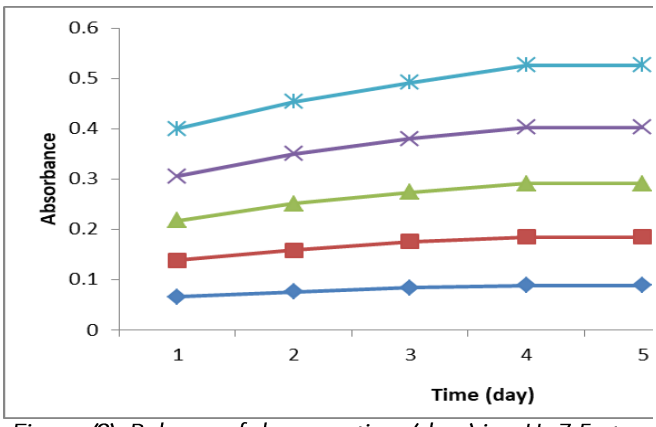


Figure (9): Release of drug per time (days) in pH=7.5 at cons. temp. 310k

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

4. Conclusions

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 6.5-7.5, whereas the endosome and lysosome are 4.5-5.5.

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