Available online at: http://brsj.cepsbasra.edu.iq

ISSN -1817 -2695

Preparation, Characterization, and Nitrofurantion Release Study of (Casein / Sodium alginate) Microparticles

Sarah A. Kamil* , Nadia A.Hussein Al-Assady*

* *Department of Chemistry, College of Education for Pure Science, University of Basrah, Basrah, Iraq.*

dr.nadia1963@gmail.com

ABSTRACT

Casein microparticales including different amounts of sodium alginate were prepared by a solvent evaporation technique, using a crosslinking agent. Microparticles were characterized based on the surface morphology, size Distribution, by photomicrographs microscopy and (FT-IR) spectroscopy. Microparticles diameters ranged between (44 - 94.4) µm. The microparticles were also evaluated in-vitro release and kinetics release of Nitrofurantoin (NFT), as a model of the drug. The results displayed that the ratios of released the NFT increase as the concentration of the loaded NFT increases on the Microparticles, and the results also show that with an increase in the Casein , sodium alginate concentration, the NFT release from the Microparaticles decreases. The (R^2) of determination indicated that the release data was within the movement of the zero order and the Higuchi equation explains that the release of the NFT is carried out according to the mechanism of diffusion. Finally , The results showed that biological efficiency for microparticle loaded with NFT exceed biological efficiency against two type bacterial *Escherichia coli* ,*Staphylococcus aurous* and one fungal *Candida albicans,* .

Key words: Casein , Sodium alginate, Nitrofurantoin, Microparticles

Introduction

Drug Delivery Systems (DDSs) based on nutritional proteins much promise due to the high food value and perfect functional properties, including emulsification, gelation, foaming and water binding capacity and also their applications as ingredients in the nutritional industry [(1)]. Food protein networks provide various possibilities to reverse linking of active molecules ,becomes they have the capacity to react with relatively wide range of active compounds through on groups on their primary structure, polypeptide that are functional the above possibilities also aim to protect the active molecules up to the extent of their release at the preferable site within the body [(2)] .Several years ago researches on microparticle carrier system brought into focus .This system is made from naturally

occurring proteins whose matrix for controlled and sustained release delivery of many drugs [3].For instance ,milk protein ,casein have centered the attention as medication carrier for the sustained delivery of cytotoxic medication [4]. microparticles made up of single polymeric materials to control drug delivery are sometimes un able to achieve all the required physical properties, encapsulation activity or even rate and mechanism of drug release[5].Thus milk proteins are widely used in nutritional industry as natural vehicles of bio actives having natural and functional characteristics ,such as casein which is inexpensive, readily available, non-toxic, highly stable and easily digestible. [6] . Its functionality in drug delivery system is facilitated via its structural and physiochemical properties including of binding ions and small molecules, exceptional surface active and stable properties, excellent emulsification and self. Assembly properties with superb gelation and water binding capacities [7]. Casein comprises about 94% protein and 6%low molecular weight compounds collectively called colloidal calcium phosphate. Four casein phosphor proteins are mainly (αs1, αs2, B- and k- casein) which exist in proportions of 4:1:4:1 by weight respectively in milk [8]. Their molecular weights range from (19-25) KDa and their average iso electric point (IP) is range from (4.6 - 4.8) the all caseins are all amphilic having ill-defined structures [9]. Casein may be used in pharmaceutical products either in form of acid which has a low aqueous solubility or sodium caseinate which is freely soluble in water but near its iso electric point [10]. Nitrofuranation(NFT){N-(5-nitro-2-furfurylidene)1- amino-hydanation } [11] Fig.(1)is a synthetic, nitrofuran-derivative antibacterial agent mainly uses in the treatment of Urinary Tract Infections (UTI) which are among the most common bacterial infections in the human [12] . NFT is often bacteriostatic but on the other hand may be bactericidal in action, depending on its concentration at the site of infection and the susceptibility of the infecting organism [13] ,as in the case of NFT is indicated for the treatment of UTI due to susceptible strains of Escherichia coli, enterococci *Staphylococcus aureus* ,and some strains of *Klebsiella* and *Enterobacter* species [14] following oral administration ,NFT is completely absorbed and rapidly eliminated by the kidneys by tubular secretion ,while 40% of the medication being excreted into the urine in the therapeutically active unchanged form[15]

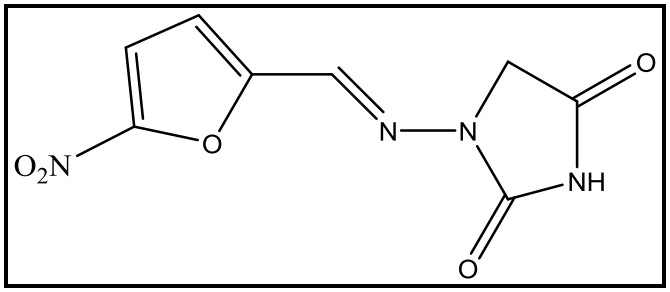

Fig.(1):The structure of Nitrofurantoin[16]

The objective of this study was to prepare and characterize Casein / Sodium Alginate microparticles containing Nitrofurantoin in alcoholic medium calcium ion was used as across linking agent. The microparticles produced were evaluated for their surface structure morphology, average particle size, drug loading activity, and drug release characteristics.

Chemical Materials and Working Methods

1. Materials

Nitrofurantoin (NFT) was provided by (NDI Co.- Iraq).Casein was provided by (NDI Co.- Iraq & India). Sodium Alginate was provided by (Fluka co.- Switzerland). Muller Hinton Agar (MHA) was provided by (Hi Media Lab co. India).

2. Methods

2. 1 Chemical Part

2. 1.1 Preparation of Casein / Sodium Alginate microparticle

The microparticles of Casein / Sodium Alginate were prepared by dissolving different weights of casein in 50ml of distilled water for 1 h at a temperature of (50) C° (Table 1). The (pH) solution was adjusted to (8 -9) with (5% w/v NaOH) solution. Different weights of sodium alginate were added to (20) ml of casein solution with constant stirring for (30) min at (25) C°. Dissolve

Nitrofurantoin in 2ml of acetone then mixed with casein solution, and it was dropped through a medical syringe into a beaker containing Cross-linking agent solution (Fig.2) was prepared from dissolution 0.5 g of $CaCl_2$ in (20) ml of mixture (12 ml of isopropanol and 8 ml of methanol alcohol) with continuous stirring with the mixer magnetic for (0.5) h and then were filtered, washed with the alcohol of isopropanol and dried at (25) C°.

Table (1): Design of the different formulations Nitrofurantoin microparticles

Batch code	Drug (g)	Sodium alginate (g)	Casein (g)
MN1	0.05	0.25	1
MN2	0.05	0.5	1
MN3	0.05	0.75	1
MN4	0.05	0.25	1.5
MN5	0.05	0.25	2
MN6	0.1	0.25	1
MN7	0.2	0.25	1

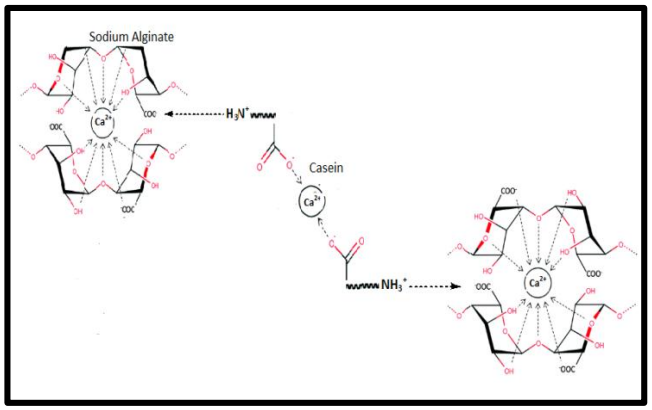

Fig. (2): Cross linking process of Casein / Sodium Alginate treated with $CaCl_2$

2.1.2 Standard calibration curve Nitrofurantoin NFT [17]

Prepare the standard stock1 solution by dissolving 100 mg NTF in to a 100ml acetone by using 100ml volumetric bottle to give a solution containing 1000µg/ml NFT. 2.5ml of the standard stock1 solution was taken and placed in a 25 ml volumetric bottle and the volume was completed to the mark with acetone to give a solution containing 100µg/ml of NFT. To determine (λ max), 0.25ml of the standard stock1 solution was taken and placed in a 25ml volumetric bottle and the volume was completed to the mark with acetone to give a solution containing 10µg/ml .the absorbance of all drug solution was measured at 360nm using (UV-spectrophotometer) in triplicate reading for avoiding any error case.

3. Characterization of Micro particles

3.1 Surface morphology study

Optical microscope was used to measure the shape and size of Casein Micro particles and diameter.

3.2. FT-IR Spectroscopy study

Record the infrared spectrum in the rang (400-3500)$cm^{-1}$of the casein, sodium alginate , drug ,blank microparticle and drug loaded microparticles, at room temperature in the shape of tablets KBr.

3.3 In vitro release studies

Simulated Gastric Fluid (S.G.F) solution is prepared by dissolving(2)gm of $CaCl_2$ in (500) ml of distilled water(H_2O), after that add (10) ml of hydrochloric acid (37%) to the previous solution and complete the result to 1000ml of distilled water(H_2O) and the pH solution was adjusted to (1.2). Simulated Intestinal Fluid (S.I.F) solution is prepared by dissolving (6.8)gm K_2HPO_4 in (250) ml of distilled water, after that adding (190) ml 0f NaOH solution (0.2M) and adding 400ml of distilled water to the mixture and the pH solution was adjusted to (8.6). after that the resulting solution with distilled water was completed to 1000ml [18]. (200)mg of prepared microparticles loaded with the Nitrofurantoin were placed in dialysis bags ,then placed in (250)ml of Phosphate Buffer Solution(PBS) pH=(7. 4), S.I.F , S.G.F after it was fixed in sterilized beaker. Each beaker was accurately covered with glass watch and fixed on magnetic stirrer at (150) rpm at (37)C° .After

different time periods take (2)ml of the samples were analyzed spectrophotometrically at (λ max 360nm)to determine the dissolved drug concentration (drug content).

3.4 In Vitro Release Kinetic Study

For the purpose of studying a mechanism of NFT release from the prepared Microparticles, the NFT release data was analyzed in accordance with the (zero order, Higuchi square root and Korsmeyer - Peppas model).

4. Biological Part

4 .1 Microbial Isolates

Three isolates where taken (two type bacterial: *Staphylococcus aurous, Escherichia coli* and one type of fungal: *Candida albicans*. Were tested for antibacterial and antifungal susceptibility .The general nutrient agar was prepared and poured into special petri dishes and then used to activate isolates, after that incubated at 37C° for 24 h for bacteria and at(28 ± 2) C° for 72 h for fungi. Inhibition of the bacterial and fungi growth were measured in Mm.

4 .2 Microbial Inoculate

A bacterial and fungicide suspension was prepared for each of the isolates and its density was measured using the McFarland barium sulfate standard 0. 5 to obtain a concentration 1×10^6CFU /mL

4.3 Antibacterial and Antifungal Assay

Extracorporeal efficiency was tasted using the diffusion method in a solid medium. Places 0.2ml of the bacterial and fungicide suspension on the surface of the *Mueller Hinton Agar* (MHA)[19-20] .Then spread it evenly over the medium using an L-shaped glass rod ,leave the plates for a period of 10 min for the suspension to be absorbed by the medium ,then perforate the plates using a cork hole to make a 7mm diameter hole add 5mg/ml/100µl to each compound in the culture medium pit for each of the isolates**.**

Result and Discussion

1 - Chemical part

1.1 FT-IR Spectroscopy

The FT-IR spectra of **NFT**, **Casein**, **Sodium alginate**, **Casein- Sodium alginate microparticles** and **Casein-Sodium alginate microparticles loaded NFT**, shown in(Fig. 3 - 7) and spectrum data gathered in Table (2).The spectrum observed that all characteristic peaks of **NFT** present in the combination spectrum, thus indicating compatibility of the **NFT** and polymer .

Table(2): Important data of FT-IR spectrums

IR Spectrum	Peaks(cm^{-1})	Groups	Deformation
NFT[21]	3479.58	N-H	Stretching
	1741.72	C=O	Stretching
	1527.62	C=C	Stretching
	1568.13	C=N	Stretching
	1436.97	NO2	Stretching
	1261.45	C-N	Stretching
	1211.30	C-O	Stretching
Casein[22-23]	3286.70	N-H,O-H	Stretching
	2924.09	C-H	Stretching
	1653.00	C=O (amide I)	Stretching
	1517.98-1541.12	N-H (amideII)	Stretching
	1072.42	C-O	Stretching
Sodium alginate[24]	3433.29	O-H	Stretching
	2935.66	C-H	Stretching
	1610.56	-COO- (Asym.)	Stretching
	1419.61	-COO- (sym.)	Stretching
	1029.99	C-O	Stretching
Casein- Sodium alginate microparticles[25]	3412.08	O-H,NH_2	Stretching
	3066.82	N-H	Stretching
	2877.79	C-H	Stretching
	887.26	C-O-C	Stretching
	1031.92	C-O	Stretching
Casein-Sodium alginate microparticles loaded Nitrofurantoin	1732.08	C=O (drug&polymer)	Stretching
	1436.97	NO_2	Stretching
	2960.73-2929.87	C-H	Stretching

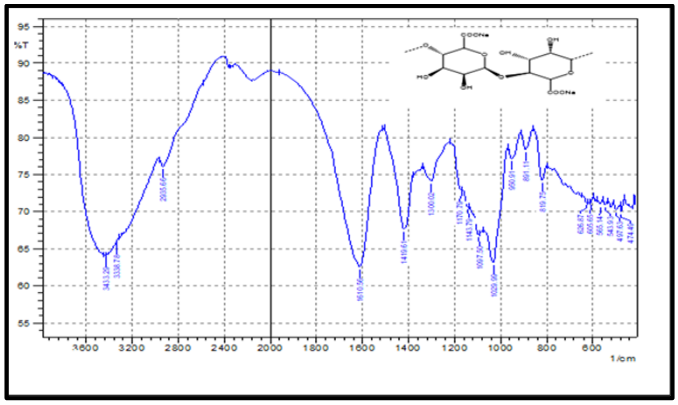

Fig.(3): The infrared spectrum of Sodium alginate

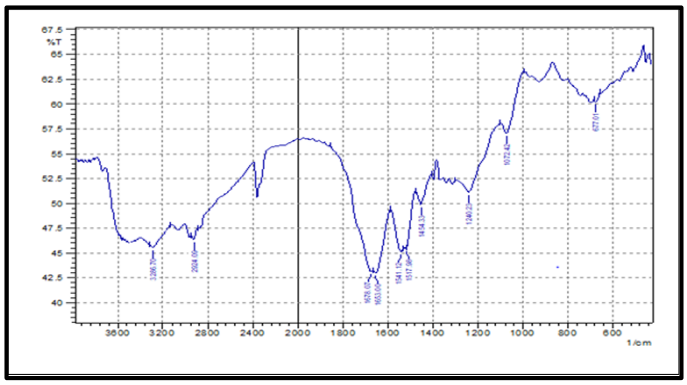

Fig.(4): The infrared spectrum of Casein

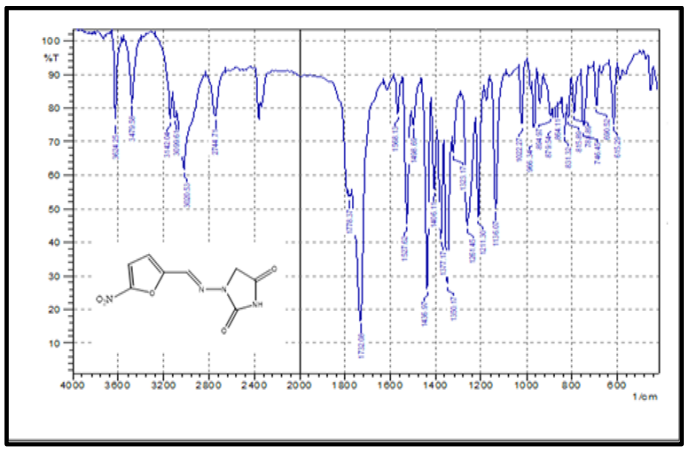

Fig.(5): The infrared spectrum of Nitrofurantoin

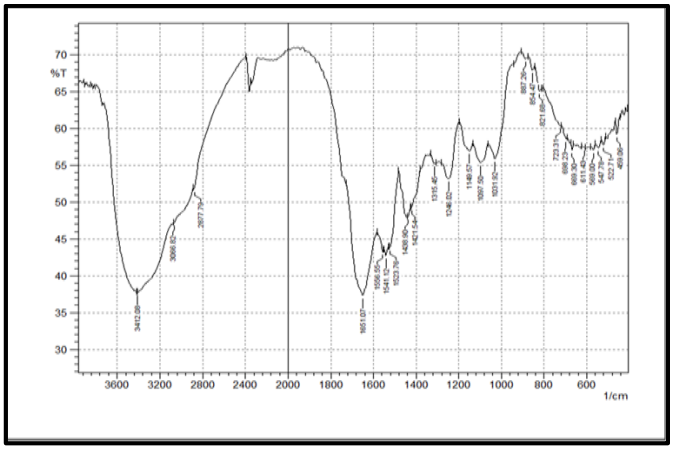

Fig.(6): The infrared spectrum of Casein- Sodium Alginate microparticle

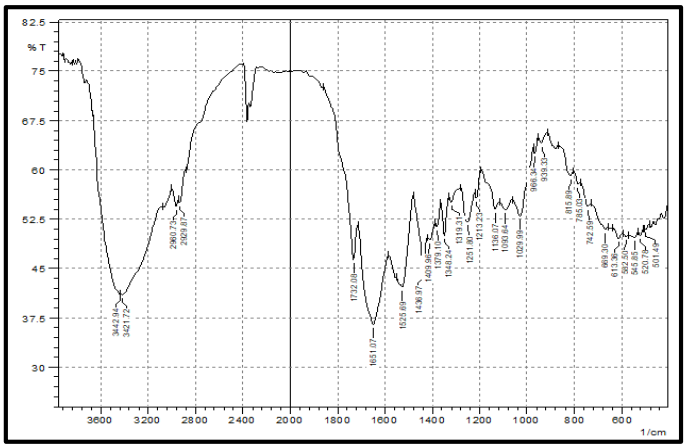

Fig.(7): the infrared spectrum of Casein- Sodium Alginate microparticle loaded Nitrofurantoin

1.2 Standard calibration curve of Nitrofurantoin NFT

After the was scanning of 10µg/ml of Nitrofurantoin NFT solution (n=3) in the UV range 320-400nm by spectrophotometer , the λ max for drug was found to be 360nm Fig.8 .The standard calibration curve of Nitrofurantoin was developed at this wave length .The calibration curve was linear between (2-20)µg /ml conc. ranges.Fig.9.

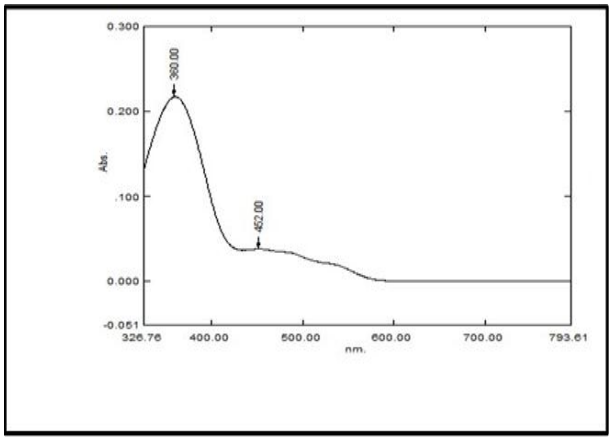

Fig.(8): λmax of Nitrofurantoin

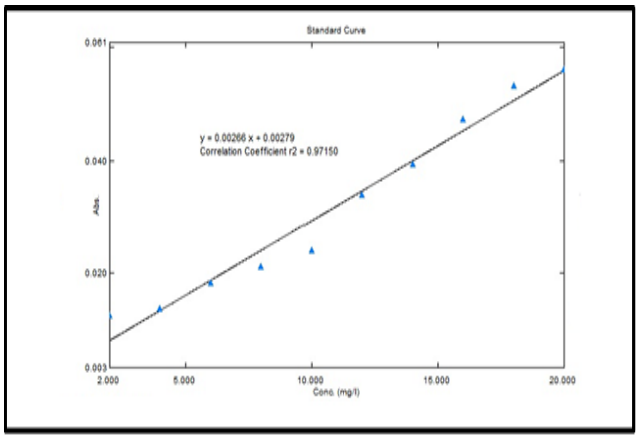

Fig.(9): Standard calibration curve graph of Nitrofurantoin

1. 3 Surface Morphology and size distribution

Microscopy was used to proof the spherical shape of the prepared microparticles [26]. It has been observed that the increased conc. of the Nitrofurantoin has increased the rough surface of the microparticles compared to the drug free for Fig.(10), a few of alginate – casein microparticles have tailing, some alginate –casein loaded NFT microparticles have tails when the casein weighs (1gm) in the prepared microparticle ,and this phenomenon because of the viscosity change. Fig. (11) and table (3) shows microparticles size.

Table (3): shows microparticles size

Batch code	Mean particale zise (µm)
MN1	66
MN2	63.2
MN3	44
MN4	52.4
MN5	46.4
MN6	74.4
MN7	94.4

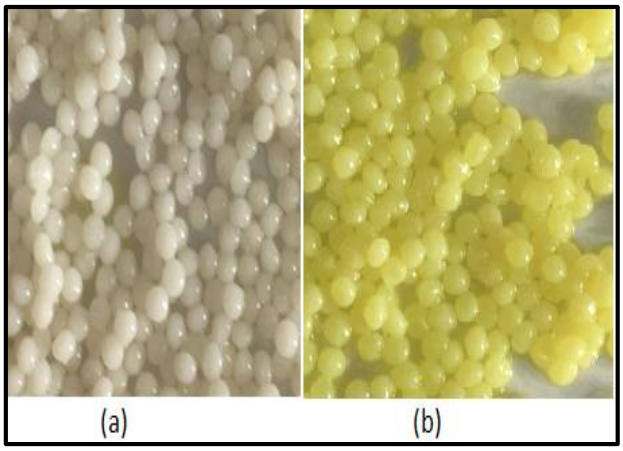

Fig.(10): Micrograph of Casein-Sodium alginate microparticles a) without drug b)with drug

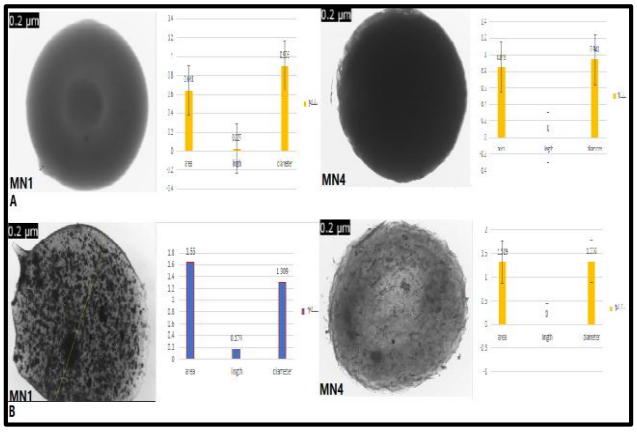

Fig.(11):(A) Optical microparticles of Casein-Sodium alginate beads (B) Casein-Sodium alginate loaded Nitrofurantoin.

1.5 In Vitro release study of NFT

200mg of prepared microparticles loaded with the **NFT** were placed in dialysis bags ,then placed in 250ml of Phosphate Buffer Solution(PBS) pH=7.4, S.I.F ,S.G.F after it was fixed in beaker. The system was placed in the Lap-Shaker at 37˚C. Three milliliters of the dispersion medium was withdrawn and filtered through 0.22 µm Millipore filters. The NFT conc. was measured at (360nm) using UV spectrophotometer .

The in vitro release profile of different Casein – Sodium Alginate conc. Microparticles formulation is shown in Fig. 12, 13. The **NFT** release-rate becomes lower when the polymer conc. increases because the smaller specific surface area of formulated larger micro particles .This shows that size is one of the effective keys for controlled release of microparticles.

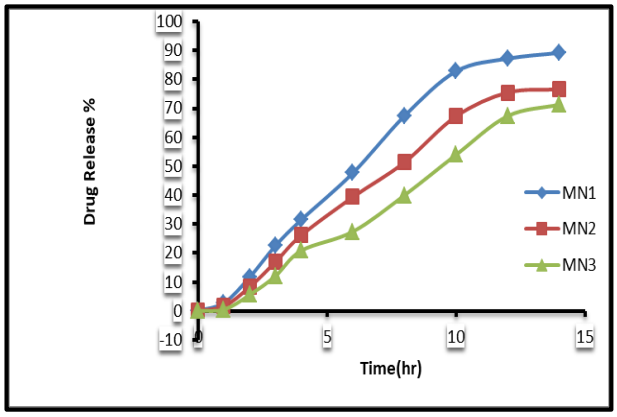

Fig.(12): Av. percentage NFT release from different Sodium Alginate conc.on microparticles in(PBS pH 7.4)at 37 C°

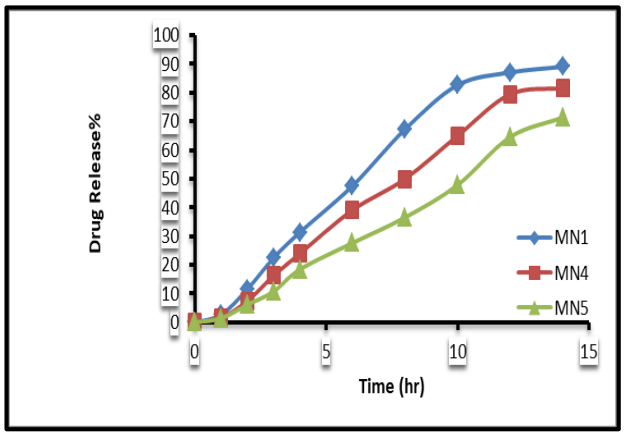

Fig.(13): Av. percentage NFT release from different Casein Conc. on microparticles in (PBS pH 7.4) at 37C °

The effect of drug loading of microparticles on NFT release from microparticles is shown in Fig. 14. It can be seen that by increasing the amount of NFT loading from 0.05 to 0.2 the rate of NFT release from the microparticles increases dramatically. With higher NFT loading, more NFT molecules are available at the surface of microparticles, leading to higher initial release.

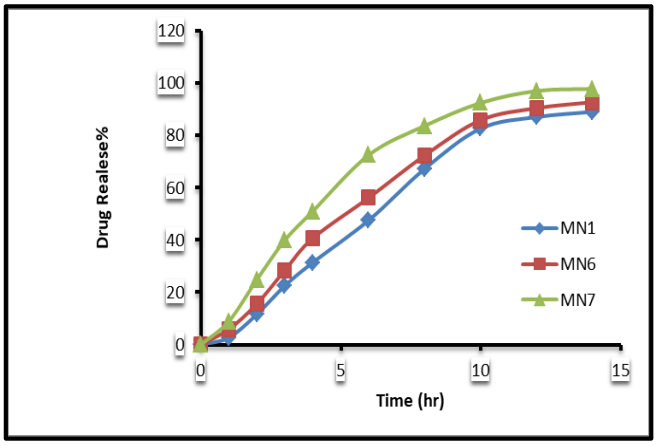

Fig.(14): Av. percentage NFT release from different NFT conc. on microparticles in(PBS pH= 7.4) at 37C°

The formulation (MN7) showed the better sustained drug release was achieved compared to the other formulations. Fig. (15) shows the percentage release curve of **NFT** from Casein- Sodium Alginate microparticles at various pH of medium (7.4, SIF ,SGF) at 37°C in different times. It can be seen that the NFT released from Casein- Sodium Alginate microparticles was (42.97%) at SGF, (89.47%) at SIF and (97.87%) pH 7.4 within 14hrs. This suggests that the drug release properties of Casein-Sodium Alginate microparticles are pH sensitive. The results suggest that the amount of **NFT** release at pH (7.4) was higher than release medium of pH (1.2). It can be correlated with swelling behavior of the casein- alginate microparticles (Fig. 16), where the swelling was increasing when pH of the medium changed from acidic to neutral.

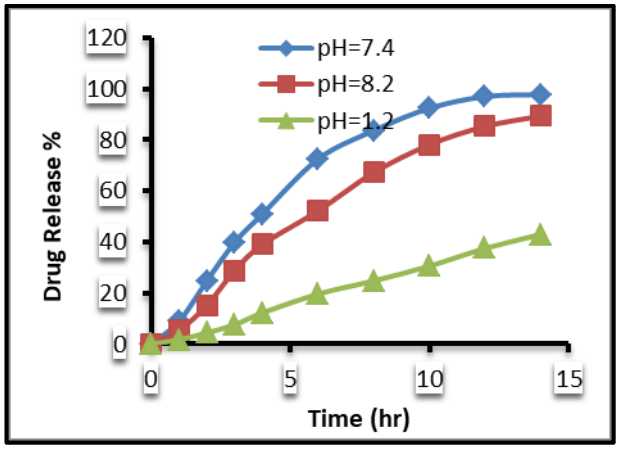

Fig.(15): Av. percentage NFT release from microparticles in different pH

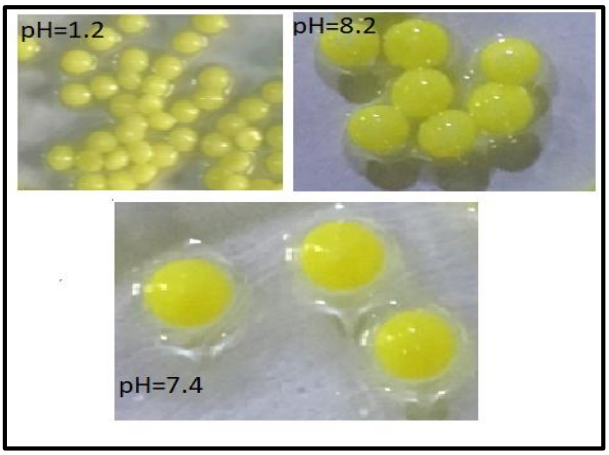

Fig.(16): Swelling behavior of the casein- alginate microparticles in different pH

1.6 Kinetics of drug release [27]

The slopes and the regression coefficient of determinations (R^2) are listed in (Table 4). The (R^2) indicated that the release data was best fitted with zero order kinetics (Fig.17-19). Higuchi equation explains the diffusion controlled release mechanism (Fig.20-22). Additional evidence for the diffusion controlled mechanism was obtained by fitting the Korsmeyer–Peppas equation to the release data (Fig.23-25). The diffusion exponent n value was found to be in range of (0.0215 to 0.8827) for different drug–polymer compositions, indicating Fickian diffusion for(less 0.5) and Non- Fickian diffusion for (above 0.5) of drug through microparticle.

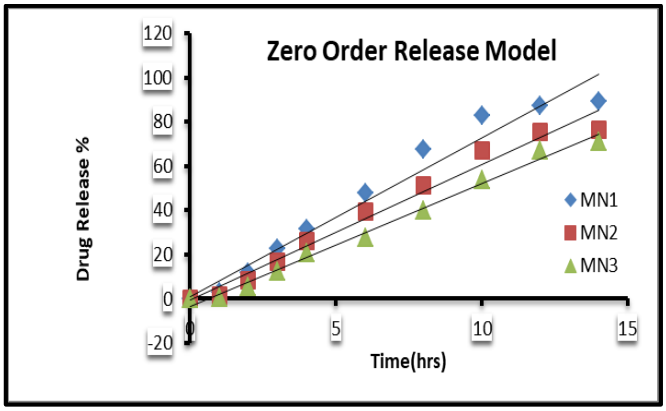

Fig. (17): Kinetic of freeing the NFT from the zero order of the microparticles when the conc. of Sodium alginate is changed

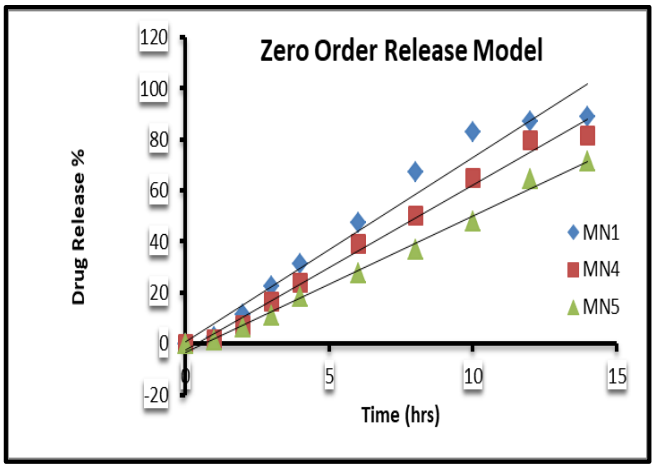

Fig. (18): Kinetic of freeing the NFT from the zero order of the microparticles when the conc. of Casein is changed

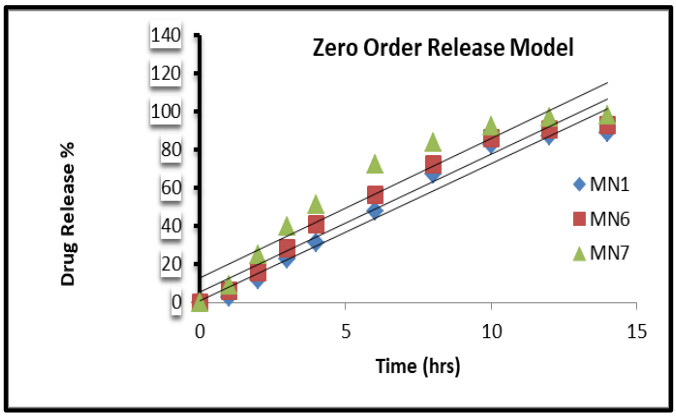

Fig. (19): Kinetic of freeing the NFT from the zero order of the microparticles when the conc. of NFT is changed

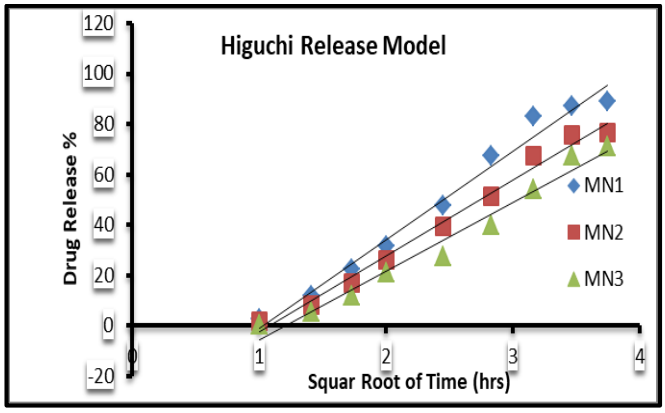

Fig.(20): Kinetic of freeing the NFT from the (Higuchi equation)of the microparticles when the conc. of Sodium alginate is changed

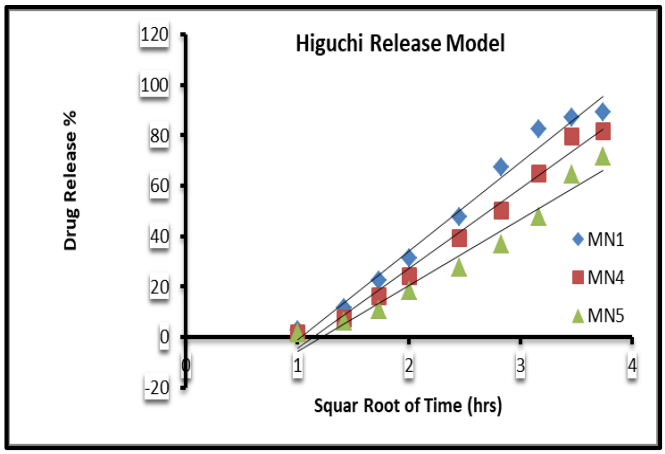

Fig.(21): Kinetic of freeing the NFT from the (Higuchi equation)of the microparticles when the conc. of Casein is changed

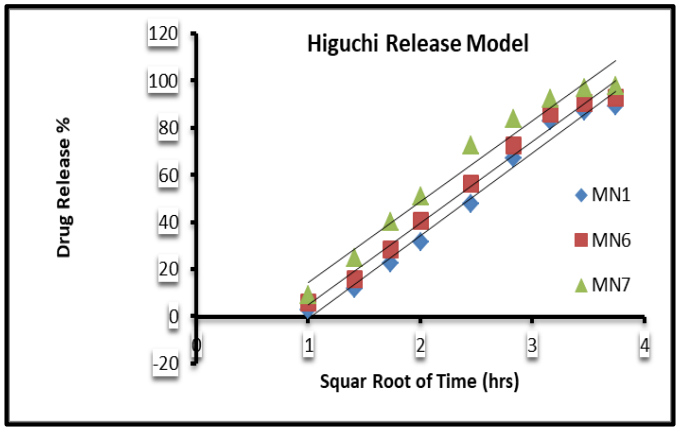

Fig.(22): Kinetic of freeing the NFT from the (Higuchi equation)of the microparticles when the conc. of NFT is changed

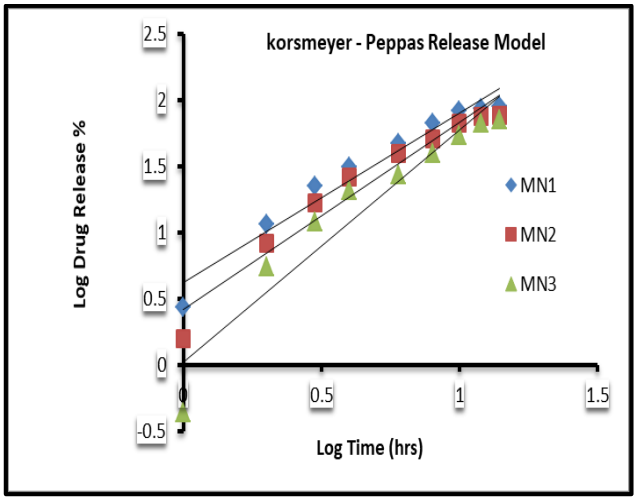

Fig. (23): Kinetic of freeing the NFT from the (Korsmeyer – Peppas equation)of the microparticles when the conc. of Sodium alginate is changed

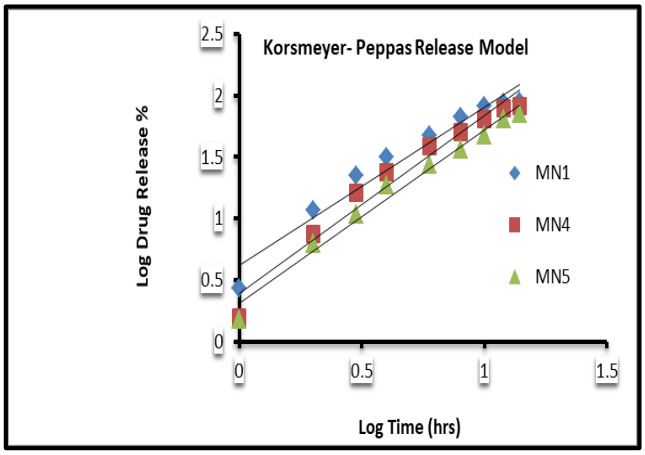

Fig. (24): Kinetic of freeing the NFT from the (Korsmeyer – Peppas equation)of the microparticles when the conc. of Casein is changed

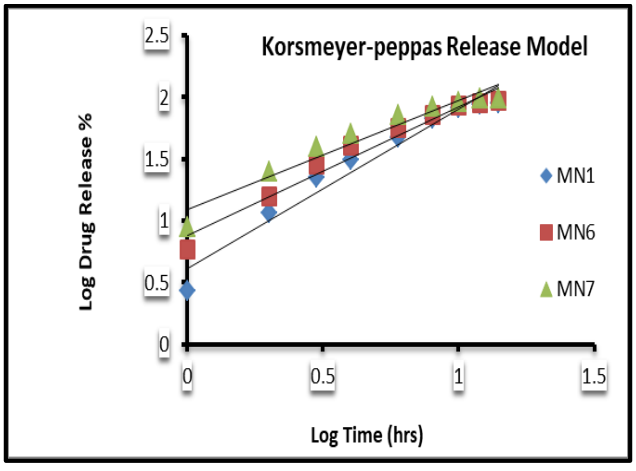

Fig.(25): Kinetic of freeing the NFT from the (Korsmeyer – Peppas equation)of the microparticles when the conc. of NFT is changed

Table (4): Correlation coefficient values for different microparticles formulations

Formulation	Zero order	higuchi model	Peppas model	
			R^2	'n'value
MN1	0.9653	0.9832	0.9542	0.6193
MN2	0.9784	0.9878	0.948	0.4188
MN3	0.9906	0.9746	0.9155	0.0215
MN4	0.9889	0.9854	0.9617	0.3918
MN5	0.9926	0.9637	0.9815	0.309
MN6	0.9534	0.9859	0.9649	0.8827
MN7	0.9062	0.9665	0.9385	0.8782

2 - Biological part

Antibacterial and Antifungal efficiency [17]

The antibacterial and antifungal efficiency were given in Fig. (26) and table (5). These formulations were evaluated for its in vitro Antibacterial and Antifungal efficiency. Note: MN (casein +sodium alginate+ drug) microparticle loaded with different conc. of NFT in the solid state], NFT(s) (Nitrofurantoin alone in the solid), M (Microparticle without drug casein +sodium alginate).

The results showed that efficiency for the NFT Micro particle exceed efficiency against three clinical isolates *Candida albicans, Escherichia coli, Staphylococcus aurous* in comparison with biological efficiency of NFT alone respectively in inhibiting all three type isolates .this is due to the increase in the biological efficiency of the polymer.

Table (5):The Inhibition Zone Diameter (Mm) for different microparticles aginst one fungal and two bacteria species

Sample	Candida albicans	Staphylococcus aurous	Escherichia coli
NFT	13	24	27
M	0	0	0
MN1	15	25	29
MN6	15	27	30
MN7	20	27	31

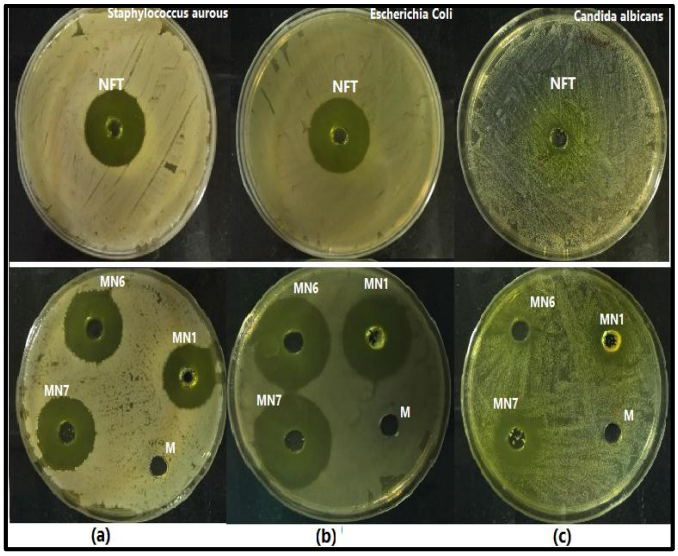

Fig.(26):Photographs show in vitro biochemical efficiency of (a) Escherichia coli ,(b)Staphylococcus aurous,(c) Candida albicans

Conclusion

Casein / Sodium Alginate microparticles of composition different amounts of Casein and sodium alginate incorporated with 0.05, 0.1 and 0.2 gm of Nitrofurantoin have been prepared in alcoholic medium calcium ion as across-linked. The optical microscopy study shows that the microparticles sizes are ranging from 44 to 94.4 µm, some Casein / Sodium Alginate loaded NFT microparticles have tails when the casein weighs 1gm. The swelling of the Casein / Sodium Alginate microparticles are in the order pH 7.4 > pH 8.2 > pH 1.2 and the increase in casein decrease the swelling percentage. The NFT release studies also follow the above order and the increase in initial drug concentration increases the rate of NFT release. The results indicated that the rate of release of the NFT was within the movement of the zero order kinetics and that the release of the drug from these microparticles is often in accordance with the mechanism of diffusion. Finally , The biological efficiency results showed that their efficacy was higher compared with activity of NFT alone

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تحضير وتشخيص ودراسة تحرر دواء النتروفورانتوين من الجسيمات الدقيقة (الكازين / الجينيت الصوديوم)

سارة عارف كامل و نادية عاشور حسين الاسدي

قسم الكيمياء ، كلية التربية للعلوم الصرفة ، جامعة البصرة ، البصرة ،العراق

الخلاصة

تم تحضير الجسيمات الدقيقة للكازين باستخدام كميات مختلفة من الجينيت الصوديوم باستخدام تقنية التبخر بالمذيبات ،باستخدام عامل التشابك شخصت الجسيمات الدقيقة على اساس هيئة السطح ، وتوزيع الحجم بواسطة التصوير المجهري للمجهر الضوئي و تقنية FT-IR . تتراوح اقطار الجسيمات الدقيقة بين (44-94.4) مايكرون . كما تم دراسة تحرر NFT وحركية تحرر النتروفورانتوين خارج جسم الكائن الحي ،كنموذج للدواء. واظهرت النتائج ان نسب تحرر الـ NFT تزداد مع زيادة تركيز الـNFT المحمل عل الجسيمات الدقيقة ، وتظهر النتائج ايضا انه مع زيادة تركيز الكازين ،الجينيت الصوديوم ينخفض تحرر الـNFT من الجسيمات الدقيقة . اشارت قيم (R2) المحددة ان التحرر يخضع لحركية المرتبة الصفرية وان معادلة هيغوشي توضح ان تحرر الـ NFT يتم وفقا لألية الانتشار, واخيرا ، اظهرت النتائج ان الفعالية البيولوجية للجسيمات الدقيقة و المحملة بـ NFT تمتلك فعالية بيولوجية تجاه نوعين من البكتيريا Escherichia coli, Staphylococcus aurous ونوع واحد من الفطريات Candida albicans .

الكلمات المفتاحية: الكازين ، الجينيت الصوديوم ، النتروفورانتوين ، الجسيمات الدقيقة