# Controlled Release of Vitamin C from Chitosan Nanoparticles

## C Vitaminin Kitosan Nanoparçacıklardan Kontrollü Salımı

Research Article

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**ABSTRACT**

This work is consisted of two parts. The first was the synthesis and characterization of nanoparticles (ChNPs) from Chitosan, a natural biopolymer. In the second part, preparation of Vitamin C loaded ChNPs and release of vitamin C from the loaded nanoparticles were investigated. ChNPs were synthesized according to the ionic gelation method and sodium tripolyphosphate (TPP) was used as the crosslinking agent. The particle size distribution of the synthesized ChNPs was determined by using Zeta Sizer. Surface morphologies and crystal structures of the nanoparticles were investigated by Scanning Electron Microscopy (SEM) and X- ray diffraction (XRD) analysis, respectively. Structural analysis and thermal properties of ChNPs were also investigated by Fournier Transform Infrared Spectroscopy (FTIR) and thermogravimetric analysis (TGA), respectively. Release porofile of the Vitamin C loaded nanoparticles at same time were determined. As a result, average particle size of the ChNPs was measured as 10 nm and loading efficiency of the ChNPs was calculated as 86% with very high vitamin C concentration. Finally, the release mechanism of vitamin C from nanoparticles was determined to be controlled by diffusion and swelling.

**Key Words**
Chitosan nanoparticles, ionic gelletion,release kinetic, vitamin C.

**ÖZ**

Bu çalışma iki aşamadan oluşmaktadır. Birinci aşama kitosanın nanoparçacıkların (ChNPs) sentezi ve karakterizasyonudur. İkincisi aşama, C vitamin yüklü ChNPS eldesi ve C vitamininin salım kinetiğinin incelenmesidir. ChNPs iyonik jelleşme yöntemine göre sentezlenmiştir. Sodyum tripolifosfat (TPP) çapraz bağlayıcı olarak kullanılmıştır. Sentezlenen ChNPs örneklerinin tanecik boyutu dağılımları, yüzey morfolojileri ve kristal yapıları sırasıyla Nanosizer, Taramalı Electron Mikroskobu (SEM) ve X-ışını difraktometresi (XRD) ile incelenmiştir. Hazırlanan ChNPs örneklerinin yapısal analizleri ve termal özellikleri sırasıyla, Fourier Transform Infrared (FTIR) spektrofotometresi ve termal gravimetrik analiz ile incelenmiştir. Aynı zamanda C vitamin yüklü ChNPs örneklerinin salım profilleri belirlenmiştir. Çalışmaların sonucunda, ChNPs örneklerinin ortalama parçacık boyutları 10 nm olarak ölçülmüştür. C vitamini yükleme verimi %86 C vitamini derişimi olarak hesaplanmıştır. Son olarak, C vitaminin ChNPs örneklerinden salım mekanizmasının difüzyon ve şişme kontrollü olduğu belirlenmiştir.

**Anahtar Kelimeler**
Kitosan nanoparçacık, iyonik jelleşme, salımı kinetiği, C vitamin.

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## INTRODUCTION

Chitosan, produced from Chitin, among the entire natural, is one of the most promising biopolymers. Chitosan is a linear copolymer which is consisted of both 2-acetamido-2-deoxy-β-d-glucan and 2-amino-2-deoxy-β-d-glucan units. These two groups with interesting physicochemical and biological properties provide the important features for biomedical applications. For example, Chitosan has been used as drug systems in many different forms such as film [1], microcapsule [2], nanoparticles [3] etc. Within these forms, many studies have been carried out to obtain chitosan nanoparticles [4-8]. Many syntheses including electrostatic complexes have been developed [9-13]. Electrostatic complexation method appears to be very charming since it allowed to detail nanoparticles nanoparticles i) with sizes in the nanometer range, and narrow size distributions, ii) in a mild environment (such as an aqueous medium). In this process, toxic cross-linking agent such as glutaraldehyde is not used to stabilize the nanoparticles. Chitosan nanoparticles formation by electrostatic complexation is depended on the cationic sites ($-NH_3^+$) available the polymer chains. If the anionic species such as citrate, sulphate or (poly)phosphate uses for the complexation of chitosan chains are molecules, the method is more specifically mentioned as "ionic gelation method" [7]. Up until now, to prepare the chitosan nanoparticles, lots of studies have been carried out with ionic gelation method, particularly by using sodium tripolyphosphate (TPP) as ionic agent [11-13].

On the other hand, Vitamin C is an imperative nutrient required to maintain the physiological process of people and some animals [14,15]. Even, Vitamin C is one of the most significant antioxidants that may decrease the risk of cancer by using various mechanisms [14,16-18]. In the same time, vitamin C is one of the most significant antioxidants that may decrease the risk of cancer by using various mechanisms [19]. This is an important anti-oxidant that may reduce the risk of cancer by neutralizing reactive oxygen species or other free radicals that can damage DNA [2,16]. Besides, vitamin C is also used in food or food additives and it has been shown to decrease LDL cholesterol in some patients [20-22]. Therefore, nano-loading systems and the release of vitamin C should continue to be developed in many applications, from food to biomedical applications.

This study was aimed to prepare and characterize ChNPs. At same time, another aim of this study was in order to load with vitamin-C to ChNPs and to investigate release of vitamin C from ChNPs.

## MATERIALS and METHODS

### Materials

Chitosan (viscosity, 200-400 mPa.s, 1% in acetic acid), Vitamin C, acetic acid ($CH_3COOH$, glacial) as used solvent and Sodium tripolyphosphate as used crosslinker were all purchased from Sigma Aldrich. All the chemicals were used without any further purification.

### Preparation of the ChNPs

The ChNPs were synthesized based upon ionic gelation method by using chitosan and TPP. Briefly, chitosan (1 mg/ml) was dissolved in 1% (v/v) acetic acid solution and NaTPP (1.75 mg/ml) were dissolved in deionized water to obtain solutions. The ChNPs were synthesized with the addition of prepared TPP solution into chitosan solution via mechanical stirring (750 rpm) at room temperature. The vitamin-C loaded- ChNPs were similarly prepared by using a chitosan solution containing the drug. 25 mg Vitamin C dissolve in chitosan solution (1 mg/ml) and prepared TPP solution (1.75 mg/ml) was added into this chitosan solution in which vitamin C was dissolved. Formed nanoparticles were reserved from solution by centrifuge at 1000 rpm for 10 min.

### Determination of Loading Efficiency

Vitamin C (25 mg) loaded ChNPs were dissolved in 100 ml 0.1 N HCl. The sample was centrifuged at 10000 rpm within 10 min and then vitamin C content was analyzed by measuring the absorbance at 244 nm ($\lambda_{max}$ of vitamin C in 0.1 N HCl) after suitable dilution using an UV spectrophotometer (PG instrument T80/80+).

$$\text{Loading efficiency (\%)} = ([\text{vitamin C}]_c / [\text{vitamin C}]_t) \times 100 \quad (1)$$

### Characterization of the ChNPs

The morphology of the samples was monitored by scanning electron microscopy (SEM). The images were obtained using 10 kV accelerating voltage. SEM images were taken at different magnifications (in the range of 1.000× and 10.000×) using Toledo University/Toledo-Ohio/US in JEOL JSM-7500F SEM instrument.

The particle sizes were determined using Zetasizer (MALVERN Zetasizer Nano Series Nano-S).

The Chitosan and ChNPs were characterized structurally by Fourier transform infrared (FTIR) spectroscopy. FTIR was used to investigate the interaction of Chitosan, TPP, and NPs. FTIR spectra were recorded by a Perkin- Elmer FTIR spectrophotometer Spectrum BX-II in the range 4,000–400 $cm^{-1}$ with the sum of 20 scans at a resolution of 4 $cm^{-1}$.

The thermal properties of the prepared samples were also analyzed with a Perkin-Elmer Diamond TG/ DTA instrument. TG/DTG profiles were performed from 30 to 600°C at a heating rate of 10°C/min under $N_2$ flow of 10 mL/min.

### In vitro release studies

Vitamin C concentration was determined using UV-Vis spectrophometrically the absorbance at 265 nm ($\lambda_{\mu ax}$ of vitamin C in PBS buffer 7.4) after suitable dilution from a calibration curve. In the experiment of determination of vitamin C concentrations, UV spectrophotometer (PG instrument T80/80+) was used. Chitosan nanoparticles equivalent to 25mg of vitamin C were taken into a cellulose dialysis bag (previously soaked in dissolution medium) containing 30ml of dissolution medium to suspend the ChNPs in the dissolution medium. The in vitro release studies of vitamin C were carried out at rinsing bath of 100 rpm in 500 mLof phosphate buffer (pH 7.4 and 25°C). 1 ml of release medium was taken at pre-determined time intervals for determining content of vitamin C. An equivalent volume of fresh dissolution medium was added in release medium after every measurement.

## RESULTS and DISCUSSIONS

### Characterization of the ChNPs

The ionic gelation using TPP as ionic agent is nowadays an appropriate method to prepare, monodisperse, and nanosize chitosan particles [11-13]. The known ionic gelation method has been composed of the ionic interaction between the protonated amino group (-$NH_3$) of CS solution and the phosphate groups (-$PO_4^{3-}$) of the anionic TPP [11-13]. Synthesized by ionic gelation method the smallest particles up to now have been obtained in this study. The avarage size of ChNPs was in rage of 20-30 nm with a broad size distruption as shown in zeta sizer output in Figure 1.

On the other hand, SEM images (Figure 2) are used to characterize the morphology and size of ChNPs. According to the SEM images of six different parts (area) of ChNPs, it has observed that all parts of ChNPs morphology has been continuous, spherical, uniform and individual particles with the approximately diameter of 10 nm with a magnification value of 300,000X. Due to the sample preparation procedure at zeta sizer, ChNPs might have aggregated together and size of nanoparticles may higher than SEM results. Another characterization method is X-Ray powder

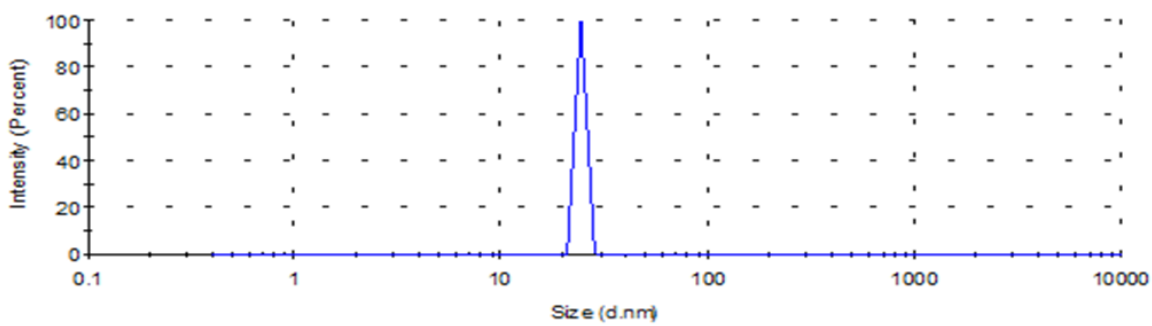


**Figure 1.** Zeta sizer diagram of ChNPs.

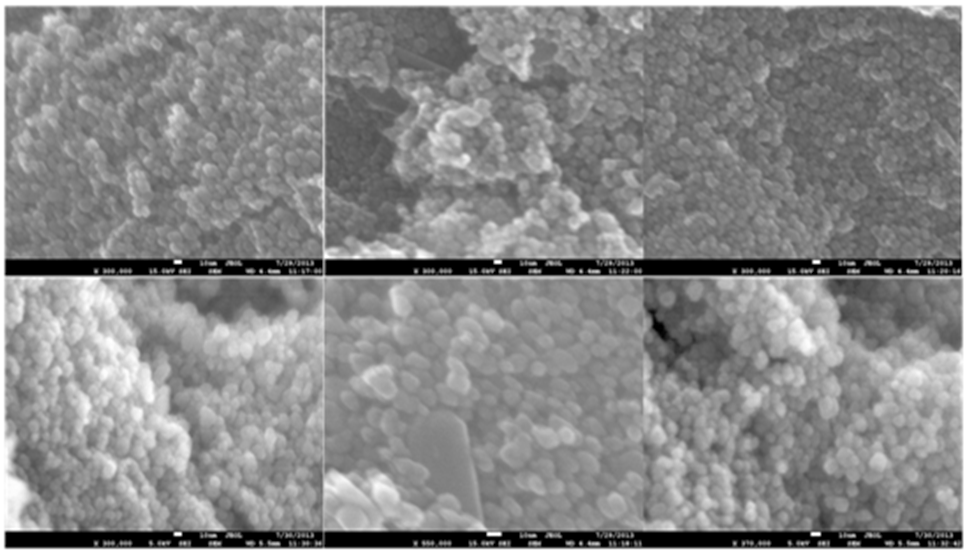

**Figure 2.** SEM analysis of ChNPs.

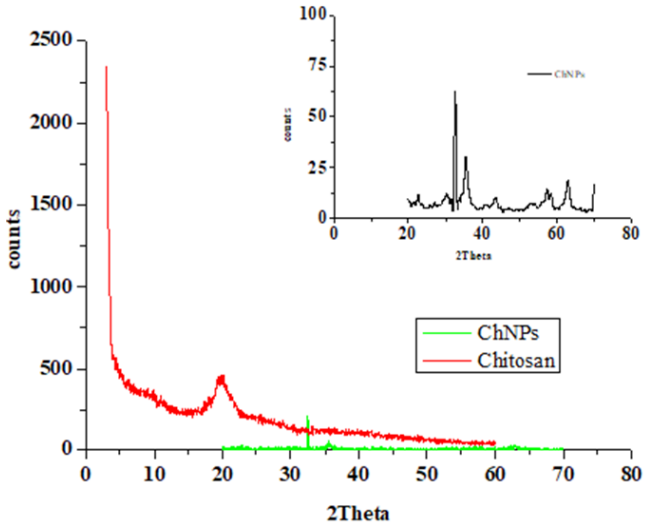


**Figure 3.** XRD pattern of Chitosan and ChNPs.

diffraction whose patterns of Chitosan and ChNPs are shown in Figure 3.

There is only one strong peak in the diffractogram of Chitosan at 2θ = 20°, indicating the high degree of crystallinity of Chitosan, its crystal lattice constant ***CrI*** corresponding to 45% [1]. Two intense narrow peaks at 2θ = 33.28° and 19.32° for TPP [23] were also observed. These peaks are related with TPP and exhibiting a high degree of crystallinity. However, in this study, two broad peaks were observed at 2θ = 32.62° and 35.56 in Figure 3, for ChNPs indicating, the crystalline nature of CS was lost due to its cross linking with TPP. Ionic interactions exist in this reaction namely an intense electrostatic interaction between the positively charged amine groups of CS and negatively charged TPP.

In accordance with Debye–Scherrer Equation, the ChNPs had an average diameter of 6.45 nm which was appropriate to SEM result for ChNPs.

In the physicochemical characterization methods, the result of FTIR spectra of chitosan and ChNPs are shown in Figure 4. The absorption bands in the spectrum of Chitosan around 1640 and 1560 $cm^{-1}$ are referred to asymmetric C=O stretching (Amide I) and N–H bending (Amide II) of acetamido groups, respectively [1]. ChNPs

are showed the presence of the P=O and P-O groups at the frequency of 1203 $cm^{-1}$ and 1239 $cm^{-1}$,respectively [23,24]. In the case of ChNPs after addition of TPP (Figure 4), the bant of amide-I was shifted to from 1653 $cm^{-1}$ to 1664 $cm^{-1}$ and N-H band in amines was shifted from 1561 $cm^{-1}$ (Amide-II) to 1549 $cm^{-1}$ representing the electrostatic interactions between the $-NH_3$ groups in CS with the phosphoric groups in TPP. Furthermore, there would also be shifting at the broad band above 3465 $cm^{-1}$ and 3186 $cm^{-1}$ corresponding to N-H and O-H bonds, respectively [23,24].

The thermal properties of Chitosan and ChNPs were determined by TG analysis as shown in Figure 5 and the thermal analysis results were presented in Table 1. There were two degradation steps on the thermograms. In Table

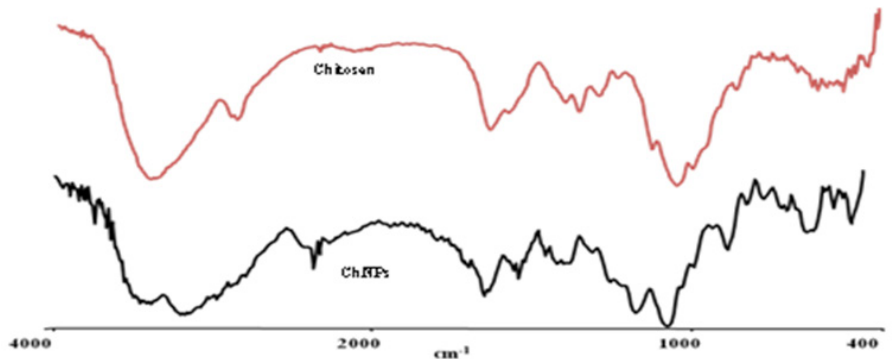


**Figure 4.** FTIR spectra of chitosan and ChNPs.

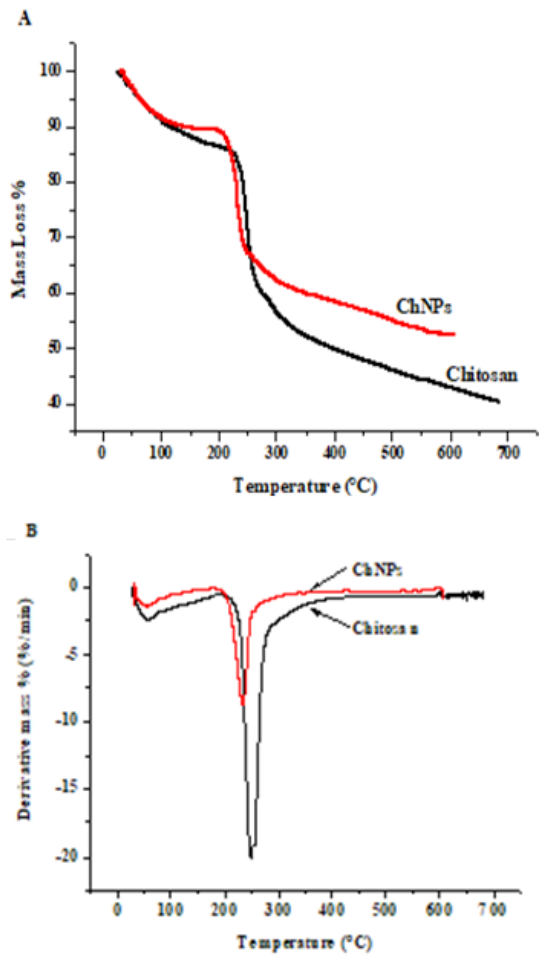


**Figure 5.** Thermogram of chitosan and ChNPs, TG curve (A), DTG curve (B).

**Table 1.** Thermal analysis results of Chitosan and CsNPs.

| | TG/DTG | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1st step | | 2nd step | | DSC | | | |
| | Mass loss (%) | T (°C) | Mass loss (%) | T (°C) | Tg (°C) | Tm (°C) | Td (°C) | ΔH (J/g) |
| Chitosan | 13 | 56.6 | 46.1 | 250 | 25 | - | 251 | -48.5 |
| ChNPs | 10 | 55.5 | 36.8 | 234 | - | 61 | 238.9 | -36.4 |

**Table 2.** Particle size and loading efficiency relationship.

| Nanoparticles size (nm) | Loading Efficiency (%) | Ref |
|---|---|---|
| 198 | 69.02 | [25] |
| 153 | ≤50 | [26] |
| 40 | n.d | [27] |
| 100 | 60-65 | [28] |
| 20 | 20 | [29] |
| 260 | 10 (theoretical) | [30] |
| 140 | Nd. | [31] |
| 250 | 80 | [32] |
| 10 | 86 | In this study |

*nd: not determined

1, the first step of mass loss was due to moisture at same temperature. On the other hand, the thermograms of ChNPs, second step mass loss was observed at 234°C in Figure 5. This degradation (36.8%) refers to the degradation of ChNPs. Besides, degradation temperature of chitosan was determined as 250°C and the mass loss was 46.1% at that temperature. It is obvious that both the degradation temperature and the amount of mass loss were decreased.

**Kinetic Study**

Vitamin C (25 mg) loaded ChNPs was used to evaluate the loading efficiency. According to the Equation 1, the loading efficiency has determined as 86%. This high efficiency is due to the low particles size. The particle size was almost 100 nm in studies carried out up to now and it has observed that the loading efficiency is lower as well. For the comparison, same experimental data obtained from cited references given in Table 2.

The five different release kinetic models have used to determine the suitable Vitamin-C release kinetic model. The results of kinetic study have given in Table 3. According to the Table 3, it can be seen clearly that first order kinetic model and Korsemeyer-Peppas model has been suitable for vitamin C release from ChNPs. The graphical peresentaion of the kinetic madels were shown in Figure 6.

First order model describes absorption and/or elimination of some drugs. This model can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices. On the other hand, Korsmeyer et al. [33,34] derived a simple relationship which described drug release from a polymeric system. The first 60% drug release data were applied in Korsmeyern Peppas model to find out the mechanism of drug release. The n value in Korsmeyer Equation is used to determine different release characterize for polymeric matrices. In this model, the n value identifies the release mechanism as described in Table 4. In this study, the n value has calculated as 0.7885 in the Table 4. According to the calculated n value, it is obviously seen that the release of vitamin C depends on swelling and diffusion control mechanism.

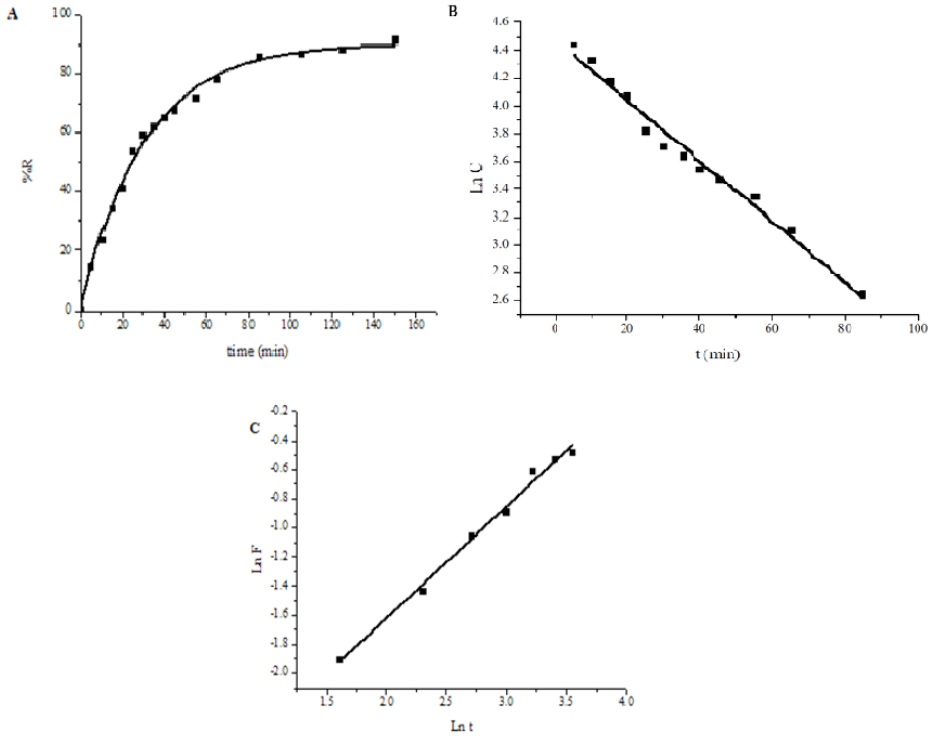


**Figure 6.** Results of release kinetic study; Release time (A), First order model (B) and Korsemeyer-Peppas model (C).

**Table 3.** Results of release kinetic study [33].

| Kinetic Model | $Q_o$(mg) | K (mg/min) | $R^2$ |
|---|---|---|---|
| Zero order | | | |
| $Q_t = Q_o + K_0 t$ | 4.14 | 0.2160 | 0.8595 |
| First order | | | |
| $InC = InC_o - Kt$ | 19.64 | 0.0219 | 0.9827 |
| Hixon-Crowell | | | |
| $Q_t^{1/3} = Q_o^{1/3} - Kt$ | 1.28 | 0.0155 | 0.9545 |
| Higuchi | | | |
| $Q = K.t^{1/2}$ | - | 2.1811 | 0.9571 |
| | n | K (mg/min) | $R^2$ |
| Korsemeyer-Peppas | | | |
| $F = M_t/M = K.t^n$ | 0.7885 | 24.66 | 0.9943 |

**Table 4.** Interpretation of diffusional release mechanisms.

| Release Exponent (n) | Drug transport mechanism | Rate as function of time |
|---|---|---|
| 0.5 | Fickian diffusion | $t^{-0.5}$ |
| 0.45 < n=0.89 | Non- Fickian transport | $t^{n-1}$ |
| 0.89 | Case II transport | Zero order release |
| Higher than 0.89 | Super case II transport | $t^{n-1}$ |

## CONCLUSION

In this study, Chitosan nanoparticles were successfully synthesized by ionic gelation method and confirmed with FTIR spectra. The improvement of crystal structure of ChNPs was estimated from XRD patterns of ChNPs. The particle size was also calculated to be 6.45 nm from XRD results. This result also has been supported by SEM images which the particles size determined as around 10 nm. The loading efficiency of vitamin C in synthesized nanoparticles has been determined as 85%. This value is stated as high efficiency for drug loading system. Release of vitamin C from CsNPs has determined as diffusion and swelling control release mechanisms by using different kinetic models.

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