



## A Novel ZnO Nanoparticle as Drug Nanocarrier in Therapeutic Applications: Kinetic Models and Error Analysis

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**Abstract:** Nanotechnology provides promising possibilities for several biomedical and pharmaceutical applications in the medical industry. Nanostructures play a major role in the recent strategies of technology suitable for novel drug applications. In this work, clindamycin phosphate (CliP) (topical anti-inflammatory drug), xanthan gum (XaG) (biopolymer) and ZnO (zinc oxide) (nanoparticle) nanostructures were synthesized using the sonochemical technique at room temperature. The characterization of the clindamycin phosphate-xanthan gum/ZnO (CliP-XaG/ZnO) nanostructure has been carried out by Fourier transform infrared (FTIR) and X-ray diffraction (XRD). The spectroscopic experiments elucidated the *in vitro* mechanism of drug delivery system at different pH media (1.2 and 7.4). In this study, the concentration of the drug in the solution was analyzed by UV-Vis spectrophotometric method and detailed error analysis were performed. The Higuchi gave the best correlation with the experimental data. The swelling behavior of the nanostructure was studied. The percentage of the swelling ratio of XaG/ZnO exerted a more significant effect than XaG at pH 1.2 and pH 7.4. The results show that the capacity of XaG / ZnO can be preferred as a novel topical anti-inflammatory drug carrier.

**Keywords:** Xanthan gum, controlled drug delivery, sonochemistry, ZnO, clindamycin phosphate.

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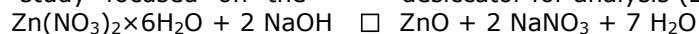
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## INTRODUCTION

In recent years, novel nanoscale materials (10 to 100 nm) are significantly used as a bio-based nanocarrier drug (nanocapsules, nanospheres, micelles, liposomes, and hydrogels) in pharmaceutical technology via storage/delivery controllable mechanism in the therapeutic application. Nanocarrier drug delivery is a progressive strategy of controlled delivery formulations and next generation of therapeutics and it develops with biocompatibility, bioavailability, targeting, and biodistribution because it has many fascinating advantages, such as reduced drug dosage, improved solubility, increased drug loading capacity, low cost, reduced unwanted chemo-toxicity, increased drug-circulation times, and minimum side effects. Metal oxide-based nanocarriers were discovered to be potent for the rising of bioavailability and biocompatibility of poorly aqueous soluble drugs and targeting (1-3).

Biopolymers such as chitosan (4), gelatin (5), alginate (6), xanthan gum (7), gum ghatti (8), and tragacanth gum (9) have been used in drug delivery mechanism owing to their excellent benefits such as biodegradability, nontoxicity, and eco-friendliness. They are employed in a great range of usages such as antibacterial agents, sensor, adsorbent, catalysis, a drug carrier, etc. (10). Physico-chemical properties can be obtained by incorporating an inorganic substance (transporting therapeutic agents) such as metal oxide nanoparticles (11), clay minerals (12), into the biopolymer matrices (13-17). Most drug carriers for drug delivery systems may cause toxicity and immune effects against carriers or therapeutic agents (18).

Xanthan gum is a linear water-soluble extracellular polysaccharide with trisaccharide provided primarily from the bacterium *Xanthomonas campestris* and has significant properties in the delivery systems, due to its biocompatible, biodegradable and non-toxic features (19-21). This study focused on the



preparation of XaG/ZnO with a controlled CliP delivery kinetics and error analysis. A CliP has an amide, an amine, and a phosphate group and is used as an antibiotic for anaerobic bacterial infections (22-23).

The primary aims of the study were to elucidate the effects of pH-sensitive XaG /metal oxide on the pharmacokinetic properties of a nanostructure, and to determine how changing the efficiency of the drug can effect in vitro drug delivery profiles. XaG was encapsulated on the surface of ZnO nanoparticles to obtain a new drug carries, and then a drug loading such as CliP was performed. The effects of ZnO nanoparticles on in vitro drug delivery profiles were studied. It was assumed that adding of ZnO nanoparticles was possible to change the anti-inflammatory drug delivery mechanism.

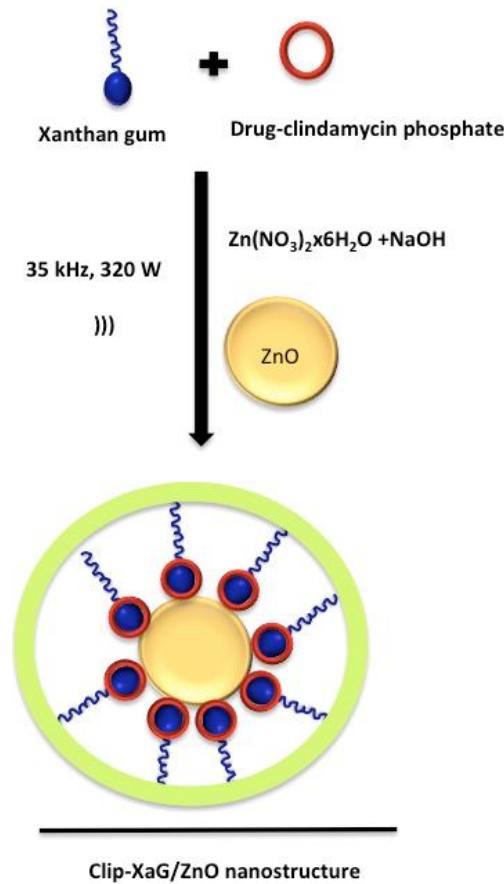
## EXPERIMENTAL SECTION

### Materials

Clindamycin phosphate ( $\text{C}_{18}\text{H}_{34}\text{ClN}_2\text{O}_8\text{PS}$ ) (ACS Dobfar Tribiano, Italy), xanthan gum (Klamar-reagent Co. Ltd., Shanghai, China), zinc nitrate hexahydrate ( $\text{Zn}(\text{NO}_3)_2 \times 6\text{H}_2\text{O}$ ) (Merck), sodium hydroxide (Merck), silica gel (Merck) and buffers (analytical grade).

### Formulation of CliP-XaG/ZnO nanostructure

CliP-XaG/ZnO nanostructures were synthesized by the sonochemical method at room temperature (frequency 35 kHz, 320 W, Sonoplus, Bandelin, Germany). A solution of XaG (0.04 g/50 mL) in water was prepared at 25 °C in an ultrasonic bath for 60 min. 10 mL of 0.002 M NaOH solution was dropped in 10 mL of 0.001 M  $\text{Zn}(\text{NO}_3)_2 \times 6\text{H}_2\text{O}$  under continuous magnetic stirring and then homogenized into an ultrasonic bath for 60 min. CliP (0.002 g/50 mL ethanol) was added into the XaG solution and then all solutions were homogenized for 60 min. The nanostructures were dried at 80 °C to a constant weight and stored at room temperature in a desiccator for analysis (24).



**Figure 1:** Synthesis of the Clip-XaG/ZnO nanostructure.

*Swelling behavior*

The swelling properties of the samples were studied at pH of 1.2 and 7.4 at 37 °C. 0.1 g of dried samples were immersed in a 50 mL solution for 6 h to reach swelling equilibrium. The swelling ratio (25-26) of nanostructures was calculated by the following formula (Eq. 1):

$$\text{Swelling ratio (\%)} = \frac{W_s - W_d}{W_d} \times 100 \quad (\text{Eq. 1})$$

$W_s$ : the weight of the swollen sample  
 $W_d$ : the weight of the dry sample

*Kinetic study of drug delivery*

In order to explain the efficacy of the nanostructure, a study of their delivery kinetics is of a major role. The kinetic model for proper the drug delivery mechanism results support to define the delivery profiles. There are several kinetic models, which calculate the overall delivery of drug from the carrier. Generally, five groups are used to understand the controlled kinetics of drug delivery mechanisms such as

empirical erosion mathematical models (Hopfenberg model and Cooney model), diffusion and chemical reaction based models (Non-Monte Carlo model and Monte Carlo model), statistical methods (Exploratory Data Analysis Method and Multivariate approach or Multivariate analysis of variance (MANOVA)), model-dependent methods (Zero-order kinetics, First-order kinetics, Higuchi model, Ritger-Peppas and Korsmeyer-Peppas model (Power law), Brazel and Peppas model, Hixson Crowell model or cube root law, Baker Lonsdale model, Peppas-Sahlin model, Weibull model, Gompertz model and Regression analysis) (Table 1), and model-independent approach. The main difference between model-independent approach (MIA) and model-dependent approach (MDA) lies in the fact that, while MIA can be calculated from the mean residence time of the drug in the dosage form, the latter requires prior adjustment of the data to a model that describes its temporal evolution. Model-dependent methods are based on different mathematical equations, are very useful to describe the release profile (27-35).

**Table 1:** A Linearized form of the kinetic models.

Equations	Kinetic models	Ref
$Q_t = Q_0 + K_0 \cdot t$	Zero order model	(29)
$\ln Q_t = \ln Q_0 + K_1 \cdot t$	First order model	(30)
$Q_t = Q_0 + K_H \cdot t^{1/2}$	Higuchi model	(31)
$Q_t = Q_0 + K_{KP} \cdot t_n$	Korsmeyer-Peppas	(32)
$Q_0^{1/3} - Q_t^{1/3} = K_S \cdot t$	Hixson-Crowell	(33)
$f_t = 3/2 [1 - (1 - M_t/M_\infty)^{2/3}] - M_t/M_\infty = k \cdot t$	Baker-Lonsdale	(34)

$Q_t$  or  $M_t$  : the amount of drug released in time  $t$ ,  $Q_0$ : the initial amount of drug,  $M_\infty$  : the amount of drug released in equilibrium.  $K_0$ : zero order kinetic constant,  $K_1$ : first order kinetic constant,  $K_H$ : Higuchi kinetic constant,  $K_{KP}$ : Korsmeyer-Peppas release constant,  $K_S$ : Hixson-Crowell kinetic constant  $n$ : diffusional release exponent  $t$  time.

#### Characterization

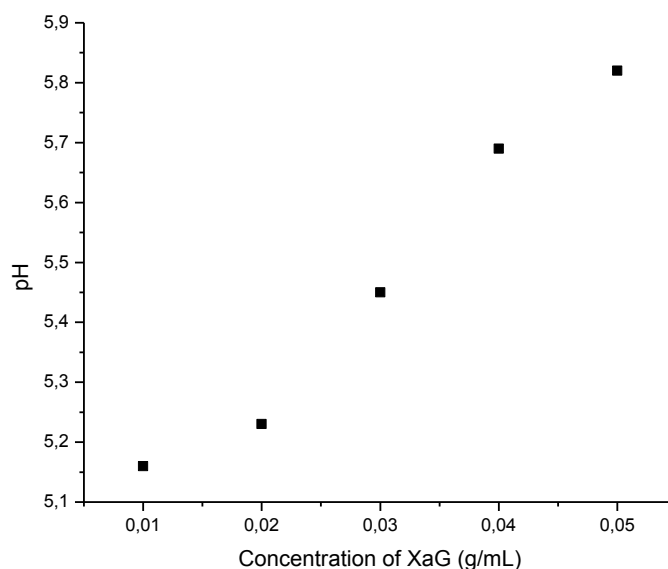
An X-ray diffractometer (Bruker D8 Advance X-ray Diffractometer) was used with  $\text{CuK}\alpha$  ( $\lambda = 0.15418$  nm, 40 kV, 40 mA) radiation over a range of  $2\theta$  angles from 2 to 75, with a step size of  $0.02^\circ/\text{s}$ . The surface morphology of nanocarrier was investigated using a Scanning Electron Microscope (SEM, Quanta FEG 450). FTIR spectroscopy was recorded using the Perkin Elmer FTIR emission spectrometer (Spectrum Two) and nanostructures were properly ground

with KBr powder and were analyzed from 4000 to  $600\text{ cm}^{-1}$  frequency range with a resolution of  $4\text{ cm}^{-1}$  and 8 scans. UV-Vis spectrophotometry was performed on Perkin Elmer (Perkin Elmer, Lambda 35) device using a pair of quartz cuvettes ( $12.4 * 12.4 * 45$  mm).

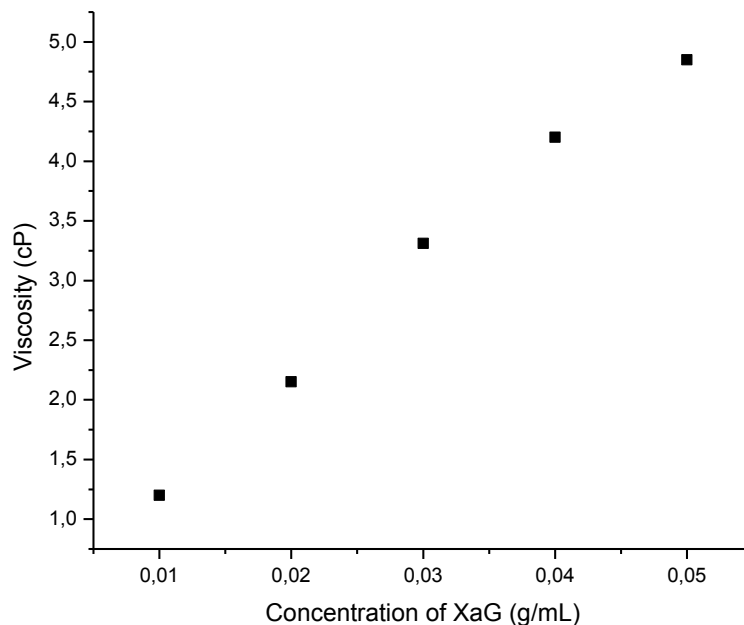
## RESULTS AND DISCUSSION

#### Swelling behavior

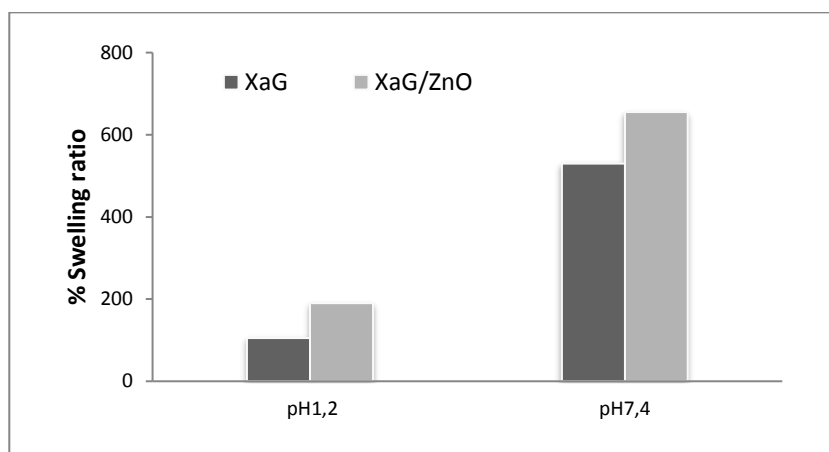
In drug delivery mechanisms the delivery rate of the pH-sensitive drug is changed with several different parameters as the swelling ratio, drug-matrix effect, amount of sample, pH, viscosity, and the initial concentration. The viscosity and pH of XaG with different concentration (0.01-0.05 g/50 mL) and the swelling ratio (SR) of XaG and Xa/ZnO in different pH buffer solutions are shown in Fig. 2-4.



**Figure 2:** The viscosity of XaG with different concentration (0.01-0.05 g / 50 mL).



**Figure 3:** pH of XaG with different concentration (0.01-0.05 g / 50 mL).



**Figure 4:** The swelling ratio of the samples.

The percentage of the swelling ratio (%) of XaG and XaG/ZnO increased with time and reached equilibrium in the 3rd hour. The swelling equilibrium values for XaG and XaG/ZnO were found as 105%, 190% at pH 1.2 and 530%, 655% at pH 7.4, respectively. The addition of ZnO in a polymer matrix increased the swelling. This result was based on the electrostatic repulsive force between functional groups and was related to the ZnO has moved as an added crosslinking agent (36).

#### Drug delivery studies

The drug delivery kinetic models for the nanostructure were applied in buffer solutions (pH 1.2 and 7.4) at  $37 \pm 0.5$  °C with continuous stirring for 6 h. As shown in Figure 1, the drug delivery shows a typical pH-sensitive delivery proceeding: faster in neutral and slower in the acidic environment and coherent with the

experimental data reported by Honglin Luo and co-workers (37).

In this study, to comprehend the drug delivery kinetic mechanism, the results were examined with different kinetic models such as zero-order kinetics, first-order kinetics, Higuchi model, Korsmeyer-Peppas model (Power law), Hixson Crowell model or cube root law and Baker Lonsdale model. Kinetic models emphasizing on different release phenomena were used to fit the drug release profile with the aid of Origin 8 software (Table 2).

In this study, the drug delivery profiles could be best explained by the Higuchi model ( $R^2 = 0.936-0.981$ ). The XaG (2.5 g/L) and XaG/ZnO (2.5 g/L) exhibited  $Q_t$  (mg/g) of 495 and 597, respectively during the initial 6 h of equilibration in neutral medium (Figs. 5-6). These values for each model

were given in Table 2. It is shown that the delivery kinetics are changed with the addition of ZnO nanoparticles which exhibited a major effect

on the rate of drug delivery. Such results of drug delivery are based on the higher surface area and distribution of nanoparticles.

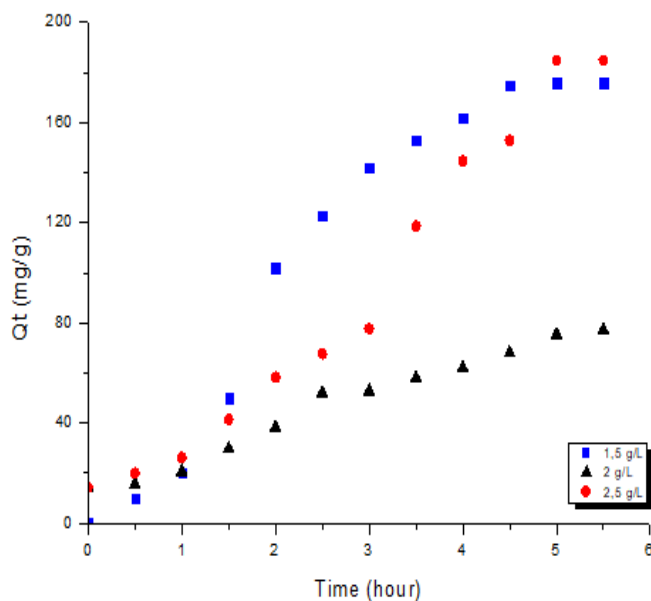


Figure 5: Amount of released drug as a function of time (1.5 g/L – 2.5 g/L of drug loaded, released at pH 1.2).

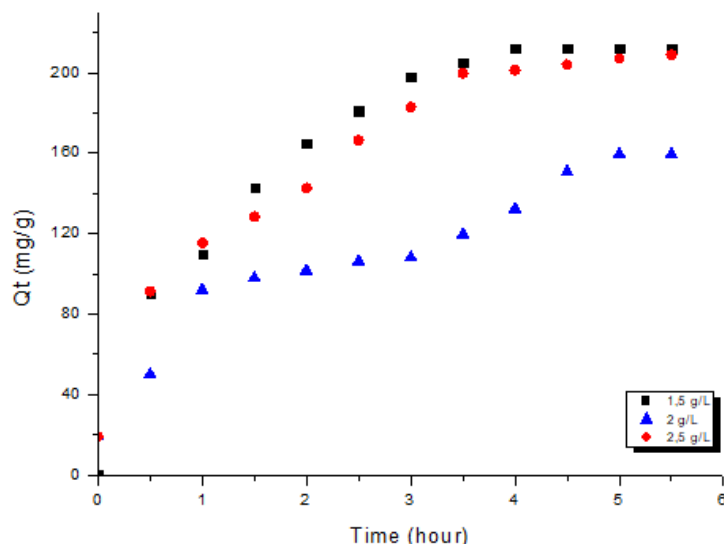


Figure 6: Amount of released drug as a function of time (1.5 g/L-2.5 g/L of drug loaded, released at pH 7.4).

**Morphology and structure**

*XRD analysis*

XRD analysis was performed to understand the morphological characteristics of a nanostructure. The XRD patterns of the XaG/ZnO and CliP-XaG/ZnO were shown in Figure 7. The size of the ZnO nanoparticle was determined using Scherr's equation (38).

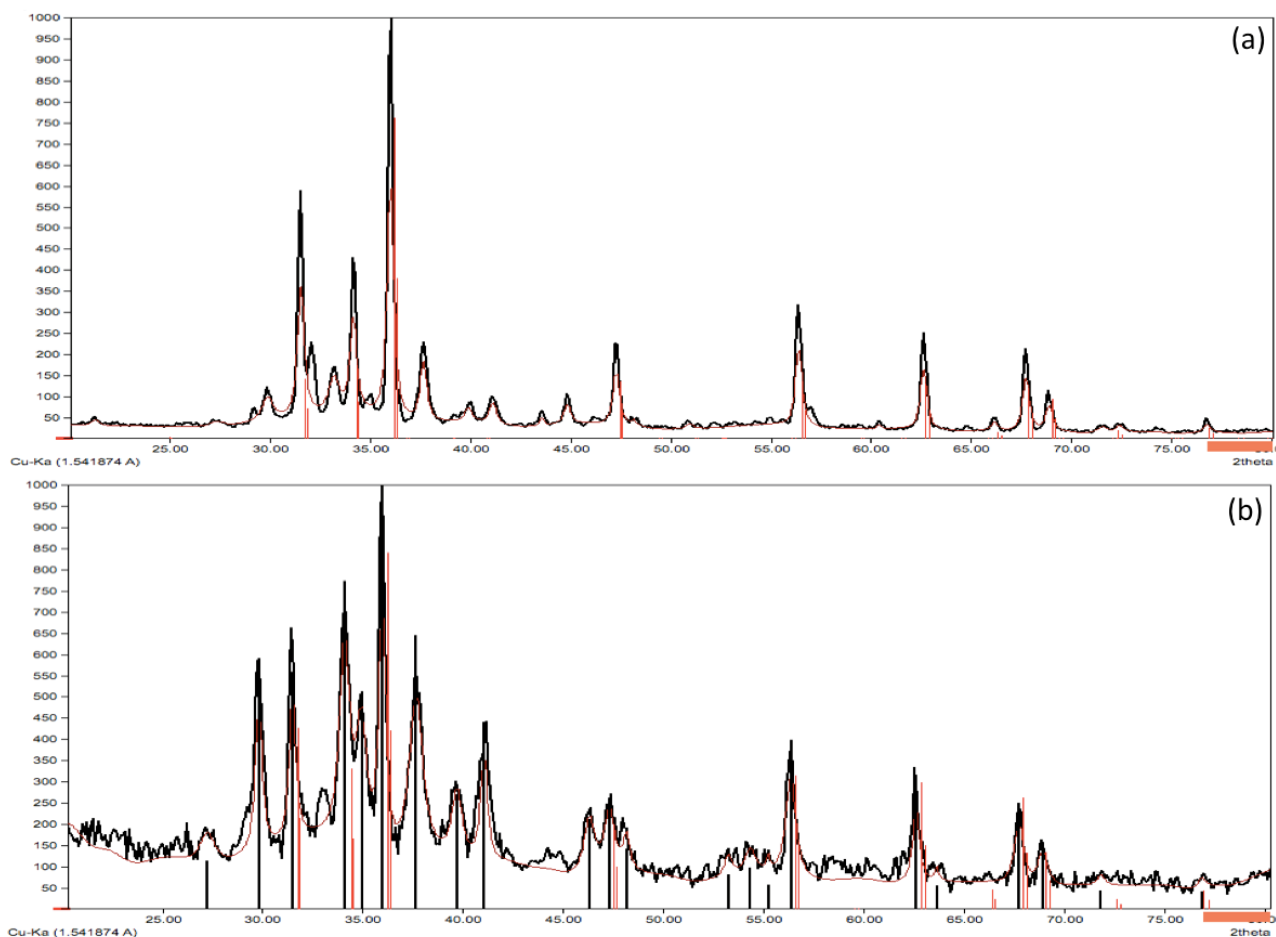
$$D = k\lambda/(\beta \text{ Cos}\theta) \quad (\text{Eq. 2})$$

where D is the crystallite size in nm, k is 0.89,  $\lambda$

is 0.154 nm and  $\beta$  is the full width at half maximum. Results match well with those of ZnO and approve the formation of ZnO nanoparticles in the polymer matrix with the support Match 3 software. In X-ray diffractogram, diffractions of ZnO peaks at a diffraction angle ( $2\theta$ ) 31°, 34°, 36°, 47°, 56°, 63° and 67° were obtained in both XaG/ZnO and CliP-XaG/ZnO. The crystallite size of ZnO is ~20 nm in CliP-XaG/ZnO.

**Table 2:** Comparison of different kinetic model parameters of clindamycin phosphate-xanthan gum/ZnO at 37 °C.

pH	g/L	Zero Order		First Order		Higuchi		Hixson-Crowell		Baker-Lonsdale		Peppas	
		R <sup>2</sup>	K (h <sup>-1</sup> )	R <sup>2</sup>	K	R <sup>2</sup>	K <sub>H</sub>	R <sup>2</sup>	K <sub>s</sub>	R <sup>2</sup>	K	R <sup>2</sup>	N
1.2	1.5	0.871	46.90	0.903	0.242	<b>0.946</b>	<b>141.39</b>	0.885	0.159	0.930	0.07	0.398	0.063
1.2	2	0.921	43.70	0.966	0.162	<b>0.936</b>	<b>192.31</b>	0.779	0.159	0.905	0.03	0.697	0.030
1.2	2.5	0.912	63.18	0.860	0.183	<b>0.963</b>	<b>204.28</b>	0.916	0.136	0.938	0.08	0.483	0.076
7.4	1.5	0.893	35.98	0.730	0.508	<b>0.965</b>	<b>130.04</b>	0.927	0.134	0.915	0.08	0.972	1.607
7.4	2	0.963	42.97	0.818	0.518	<b>0.986</b>	<b>147.71</b>	0.974	0.111	0.891	0.07	0.967	1.433
7.4	2.5	0.967	85.02	0.833	0.558	<b>0.981</b>	<b>289.95</b>	0.975	0.1741	0.676	0.06	0.972	1.6071



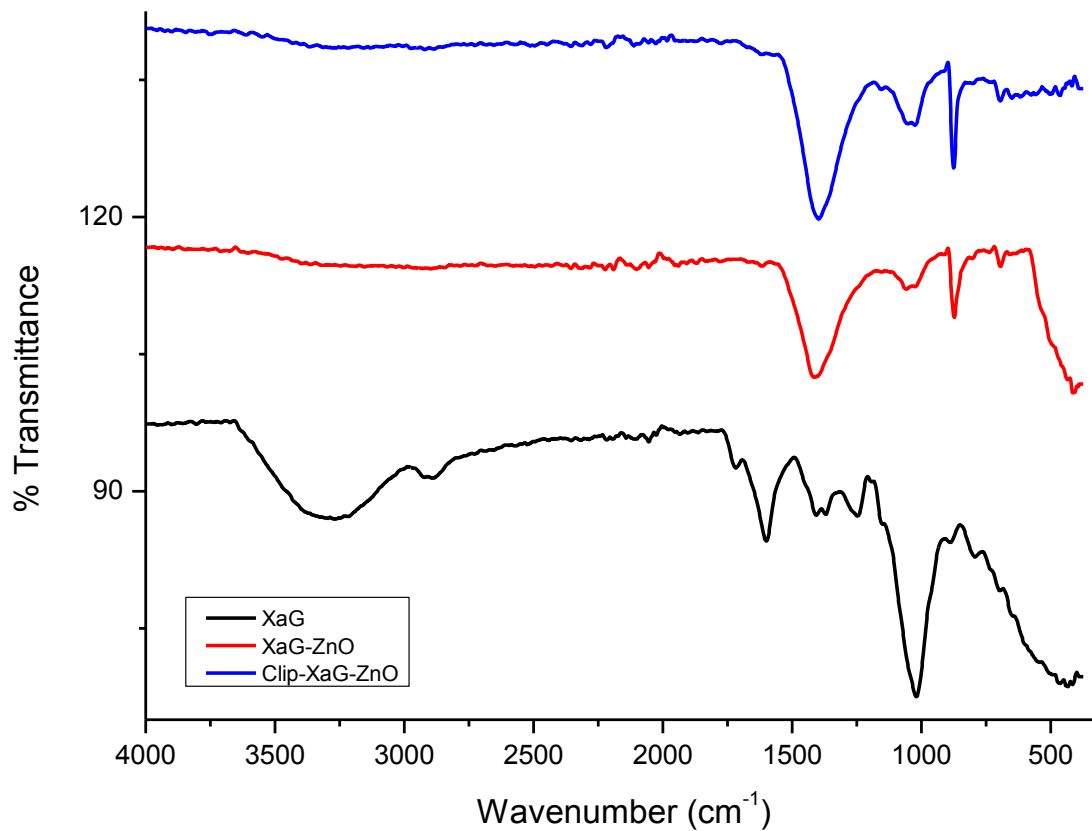
**Figure 7:** The XRD pattern of XaG/ZnO (a) and ClIP-XaG/ZnO (b).

#### FTIR analysis

The chemical interactions between drug and XaG-ZnO nanoparticles were studied by FTIR analysis (Figure 8). In FTIR spectra, all the characteristic peaks of XaG were observed at  $3267\text{ cm}^{-1}$  (-OH), at  $1594.4\text{ cm}^{-1}$  (C=O stretching) and at  $1369.7\text{ cm}^{-1}$  (C-H stretching) peaks. FTIR spectrum of

XaG-ZnO was found a very intense band below  $500\text{ cm}^{-1}$  related to the stretching vibration of ZnO bond and was observed at  $1690.6\text{ cm}^{-1}$  (C=O stretching),  $1620.5\text{ cm}^{-1}$  (C=C stretching),  $1350.8\text{ cm}^{-1}$  (C-H bending) peaks which are in agreement with Hashemi et al. (39) and Benichou et al. (40).



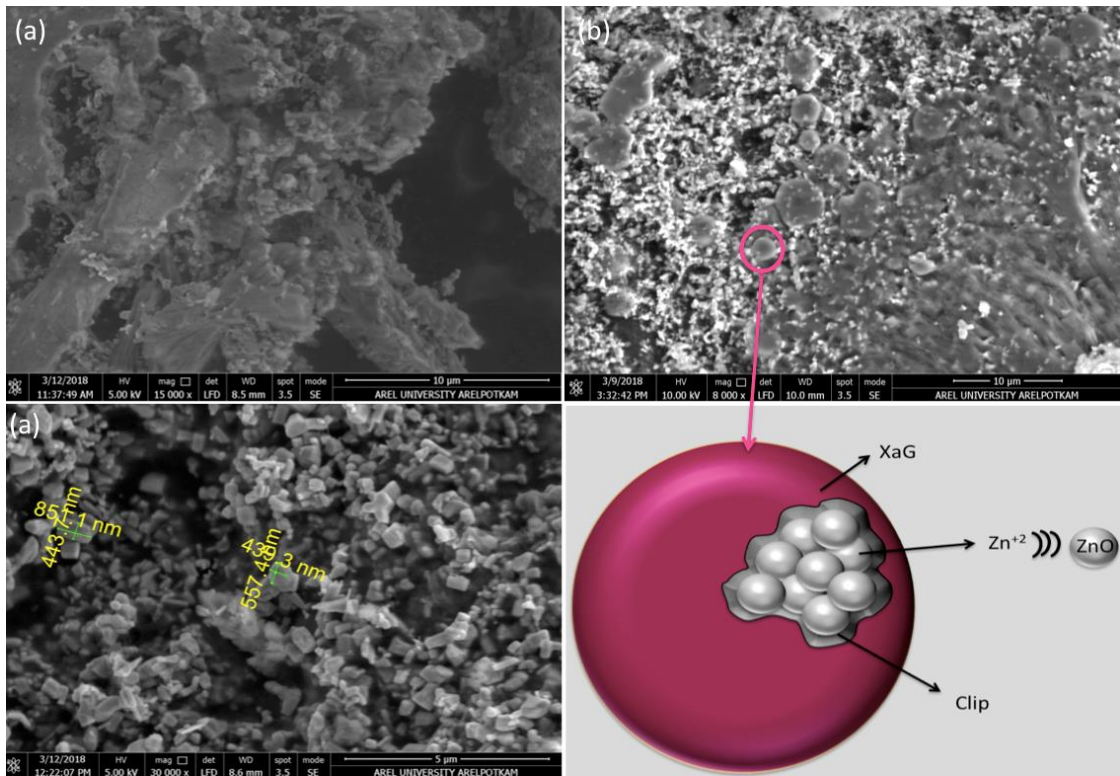


**Figure 8:** Infrared spectroscopy (ATR-IR) data for XaG, XaG/ZnO and Clip-XaG/ZnO.

#### SEM analysis

The Scanning electron microscope (SEM) micrographs performed on the internal structure was used to observe the distribution of the ZnO particles in the XaG and Clip-XaG (Fig.9). It was monitored that the hydroxides on the surface of the ZnO particles tended to interact with XaG as a cubic structure at a diameter larger than 443

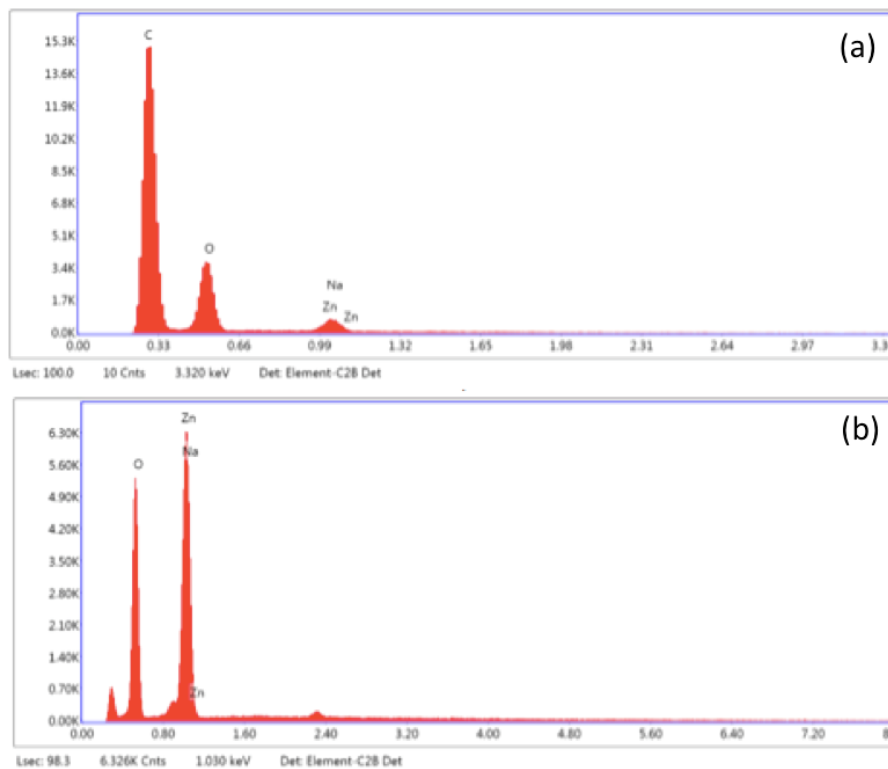
nm and to interact with Clip-XaG as a spherical structure. And also a relatively well dispersion of ZnO nanoparticles in drug-polymer matrix was observed. The experimental results showed that the drug-polymer matrix encapsulated some of the ZnO particles through van der Waals coagulates.



**Figure 9:** SEM images on the surface of (a) XaG/ZnO and (b) CliP-XaG/ZnO.

The SEM-EDX mapping of Zn, C and O elements on the surface of the samples shown in Figure 10

approve the dispersal of ZnO nanoparticles and the formation of nanostructures.



**Figure 10:** SEM-EDX spectra of (a) XaG/ZnO and (b) CliP-XaG/ZnO.

**Error analysis methods of kinetic models**

The application of  $R^2$  is not enough to understand linear drug delivery kinetic models, which evaluates the distinction between experimental and theoretical data. Therefore, we calculated

five error analysis methods for identifying of model parameters in this study which were the sum of squares of errors (SSE), The hybrid fractional error function (HYBRID), Marquart’s percentage standard deviation (MPSD), The

average relative error (ARE), and the sum of the absolute errors (EABS), respectively (Table 3) (41-45).

**Table 3:** The names and equations of error analysis methods.

Equations	Error models	Ref
$\sum_{i=1}^n (q_{e,calc} - q_{e,meas})_i^2$	SSE	(41)
$\frac{100}{n-p} \sum_{i=1}^n \left[ \frac{(q_{e,meas} - q_{e,calc})_i^2}{q_{e,meas}} \right]$	HYBRID	(42)
$100 \sqrt{\frac{1}{n-p} \sum_{i=1}^n \left( \frac{q_{e,meas} - q_{e,calc}}{q_{e,meas}} \right)_i^2}$	MPSD	(43)
$\frac{100}{n} \sum_{i=1}^n \left  \frac{q_{e,meas} - q_{e,calc}}{q_{e,meas}} \right _i$	ARE	(44)
$\sum_{i=1}^n  q_{e,meas} - q_{e,calc} _i$	EABS	(45)

qe,meas: measured capacity,  
 qe, cal:calculated capacity,  
 n: number of data points  
 p: number of parameters.

In this study, we understand that the most clear result from these models is the Higuchi kinetic model in the lowest amounts for the error parameters (Table 4) and therefore fits the data better than the rest of the drug delivery kinetic models.

**CONCLUSIONS**

Comparison of the drug delivery rate profiles of XaG/ZnO by using different types of models showed the highest Qt (mg/g) of the drug carrier at pH 7.4. The parameters of a kinetic model are that the kinetic mechanism displays just diffusion controlled drug delivery from non-degradable panels, the drug is first distributed in a homogeneous phase. The experimental data show that the capacity of XaG/ZnO can be preferred as a novel topical anti-inflammatory drug carrier.

**Table 4:** Error analysis of the different kinetic models of clindamycin phosphate-xanthan gum/ZnO.

pH		Zero Order	First Order	Higuchi
1.2	SSE	178395,6	139434,9	<b>840,85</b>
	HYBRID	492,34	360,19	<b>370,56</b>
	MPSD	1,54	1,63	<b>0,08</b>
	ARE	2,12	2,76	<b>1,5</b>
	EABS	718,58	821,24	<b>536,5</b>
7.4	SSE	291080	398745	<b>970,85</b>
	HYBRID	706,48	900,596	<b>320,56</b>
	MPSD	2,34	2,74	<b>0,07</b>
	ARE	2,65	2,86	<b>1,2</b>
	EABS	828	937	<b>345,6</b>

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