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Loaded of Etodolac on Zinc Oxide Nanoparticles

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ABSTRACT

Etodolac, a chiral nonsteroidal anti-inflammatory drug (NSAID), is widely used for pain management and arthritis treatment. However, it suffers from various side effects, including gastrotoxicity and cardiovascular risks. This study investigated the potential of zinc oxide nanoparticles (ZnO NPs) as a delivery platform for etodolac to improve its efficacy and mitigate these adverse effects.

ZnO NPs possess several attractive properties for drug delivery applications, including low toxicity, biodegradability, and the ability to target specific tissues. In this study, etodolac was successfully loaded onto ZnO NPs, and the resulting nanocomposites were characterized using Fourier-transform infrared spectroscopy (FT-IR) and scanning electron microscopy (SEM).

FT-IR analysis confirmed the successful loading of etodolac onto the ZnO NPs. Additionally, SEM images revealed morphological changes on the surface of the nanocomposites compared to pure ZnO NPs, further indicating successful drug loading.

These findings demonstrate the feasibility of developing etodolac-loaded ZnO NPs as a promising approach for targeted drug delivery. Further studies are warranted to investigate the vivo efficacy and safety of these nanocomposites, paving the way for their potential clinical application.

تحميل الإيتودولاك على جزيئات أكسيد الزنك النانوية

زينب عبد الامير حسين ، رجوان عبد الجبار غزاي ، نهاوند حامد

الملخص

يستخدم الايتودولاك وهو عقار مضاد للالتهابات غير الستيرويدي، على نطاق واسع لإدارة الألم وعلاج التهاب المفاصل. ومع ذلك، فإنه قد يسبب آثار جانبية مختلفة، بما في ذلك تسمم المعدة ومخاطر القلب والأوعية الدموية. بحثت هذه الدراسة في إمكانات استخدام الجسيمات النانوية كمنصة لتوصيل الإيتودولاك لتحسين فعاليته والتخفيف من هذه الآثار الضاره .

تمتلك الجسيمات النانوية لأكسيد الزنك العديد من الخصائص المهمة لتطبيقات توصيل الأدوية، بما في ذلك السمية المنخفضة، والقابلية للتحلل البيولوجي، والقدرة على استهداف أنسجة معينة. تم تحميل الإيتودولاك بنجاح على الجزيئات النانوية لاوكسيد الزنك وتم تشخيص المركبات النانوية الناتجة باستخدام التحليل الطيفي للأشعة تحت الحمراء لتحويل فورييه والمجهر الالكتروني الماسح.

اكد تحليل الاشعة تحت الحمراء على نجاح تحميل الايتودولاك على سطح جزيئات أكسيد الزنك النانوية بالاضافة الى ذلك كشفت صور المجهر الالكتروني عن تغيرات شكلية على سطح المركبات النانوية مقارنة ب جزيئات أكسيد الزنك النانوية النقية مما يشير الى نجاح عملية تحميل الدواء.

توضح هذه النتائج جدوى تطوير جزيئات أكسيد الزنك النانوية المحملة بالإيتودولاك كنهج واعد لتوصيل الأدوية المستهدفة. هناك ما يبرر إجراء المزيد من الدراسات للتحقيق في فعالية وسلامة هذه المركبات النانوية، مما يمهد الطريق لتطبيقها السريري المحتمل.

1. INTRODUCTION

Etodolac 1.8-diethyl- 1,3,4,9-tetrahydropyran (3.4-B)indole-l-acetic acid as shown in figure1. Etodolac is a White crystalline compound, practically insoluble in water but soluble in Alcohol, chloroform, dimethyl sulfoxide and aqueous polyethene glycol(Haldorai and Shim, 2014)The Etodolac main action is blocking the prostaglandin chemokines action which plays an important role in process of inflammatory. Etodolac possesses several unique disposition features mainly due to its stereoselective pharmacokinetics. In plasma, the concentrations of the 'inactive' R-enantiomer are about 10-fold higher than those of the active S-enantiomer, an observation that is novel among the chiral NSAIDs.

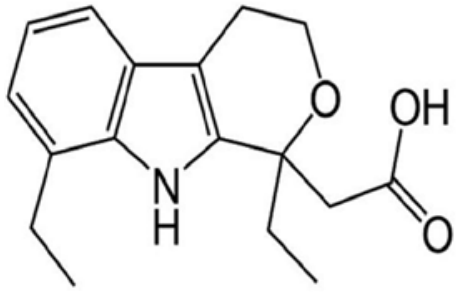

Figure 1. Structural Formula of Etodolac

In common with other NSAIDs, the drug is highly plasma protein bound and undergoes virtually complete biotransformation to oxidised metabolites and acyl-glucuronides. Etodolac is well absorbed, with maximal plasma concentrations attained within 1 to 2 hours in healthy volunteers. The elimination half-life of Etodolac is between 6 and 8 hours in plasma and is similar for both enantiomers (Sutapa *et al.*, 2018)

NSAIDs are used for the management of mild to moderate pain, fever, and inflammation. They work by reducing the levels of prostaglandins, which are chemicals that are responsible for pain and the fever and tenderness that occur with inflammation. Etodolac blocks the cyclooxygenase (COX) enzymes which form prostanoids, resulting in lower concentrations of prostaglandins .(Seay and Elim, 2019)

As with many nonsteroidal anti-inflammatory drugs (NSAIDs), Etodolac has side effects, such as gastrotoxicity, and cardio-Vascular risk. Formulation of etodolac Nanoparticles may reduce these side effects and help to target the active substance for better efficacy (Haldorai and Shim, 2014)

The Nano derives from the Greek word "nanos", which means extremely small.1 . The drug is dissolved, entrapped, encapsulated (or) attached to a nanoparticle matrix. The materials which are used for the preparation of nanoparticles should be nontoxic, biodegradable, sterlizable etc. The types of nanoparticle Nanospheres: Nanospheres are matrix systems in which the drug is physically and uniformly dispersed. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane. The goal of using this nano is to control the particle size, surface properties and release of pharmacologically active agents to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen((Çırpanlı *et al.*, 2009), (Brocks and Jamali, 1994)). Nanoparticles are widely used Because of their unique properties and promising applications as anti-cancer and antimicrobial agents the material properties change as their size approaches the Atomic scale. This is due to the surface area to volume ratio increasing, resulting in the material's surface atoms dominating the material's performance. Owing to Their very small size, nanoparticles have a very large Surface area to volume ratio when compared to bulk materials, such as powders, plates and sheets. This Feature enables nanoparticles to possess unexpected Optical, physical and chemical properties, as they are small enough to confine their electrons and produce quantum effects .(Kirkby *et al.*, 2013)

For the past few decades, there has been considerable research interest in the area of drug delivery using particulate delivery systems as carriers for small and large molecules. Particulate systems like nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. They have been used in vivo to protect the drug entity in systemic circulation, restrict access of the drug to the chosen sites and deliver the drug at a controlled and sustained rate to the site of action. Various polymers have been used in the formulation of nanoparticles for drug delivery research to increase therapeutic benefit while minimizing side effects (Biswal, 2020).

One of the most promising directions is to use zinc nanoparticles for molecular diagnostics, target delivery of drugs, and developing new pharmaceutical preparations (Jain, 1997). The zinc nanoparticles possess unique semiconducting, optical, and piezoelectric properties, so it has been investigated for A wide variety of applications. One of the most important features of ZnO nanometers is low toxicity and biodegradability. Biomedical Applications Of ZNO nanoparticle ZnO NPs, as a new type of low-cost and low toxicity. Nanomaterials have attracted tremendous interest in various Biomedical fields, including anticancer, antibacterial; diabetic, and anti-inflammatory activities, as Anti-oxidant well as for drug delivery and bioimaging applications ((Soenen *et al.*, 2015), (Mohanraj and Chen, 2006)). Depending on these facts Etadolac was loaded on the ZnO nanoparticle's surface as a drug delivery system in this research.

2. The Experimental Part

2.1 Materials and Instruments

All the chemicals are of high purity, commercially available AR grade. All the chemicals are of high purity, commercially available AR grade. Ethanol solvent was supplied by Hi-Media, India. The ZnO nanoparticles are purchased from MKnano, Canada. Etodolac from SDI-Samara, Iraq

Table 1: The Instruments

Device	Company	Origin
Electric balance	Sartorius	Germany
Magnatic Stirrce	National	Japan
PH_meter	Mauritius	Germany
Infrared spectroscopy	Shimadzu	Japan
Electronic Microscope	FEI Quanta450	Czech Republic

2.2 Method

Preparation of Etodolac-Loaded Zinc Oxide Nanoparticles

The 0.02g pure Etodolac is dissolved in 50ml ethanol in a beaker and added to 1g of zinc oxide nanoparticles. The pH of the solution is adjusted to 7 by HCl. The ethanolic solution of the Etodolac drug and zinc oxide nanoparticles is stirred for 72 hours in a stirring device. The collected samples are filtered, and the prepared Etodolac conjugate zinc nanoparticles are collected.

2.3 The Fourier Infrared Spectroscopy

To characterize, and determine functional groups and modifications the FTIR spectroscopy performed for pure-ZnO-NPs, Etodolac and ZnO-NPs- Etodolac
as shown in figures (2,3,4).

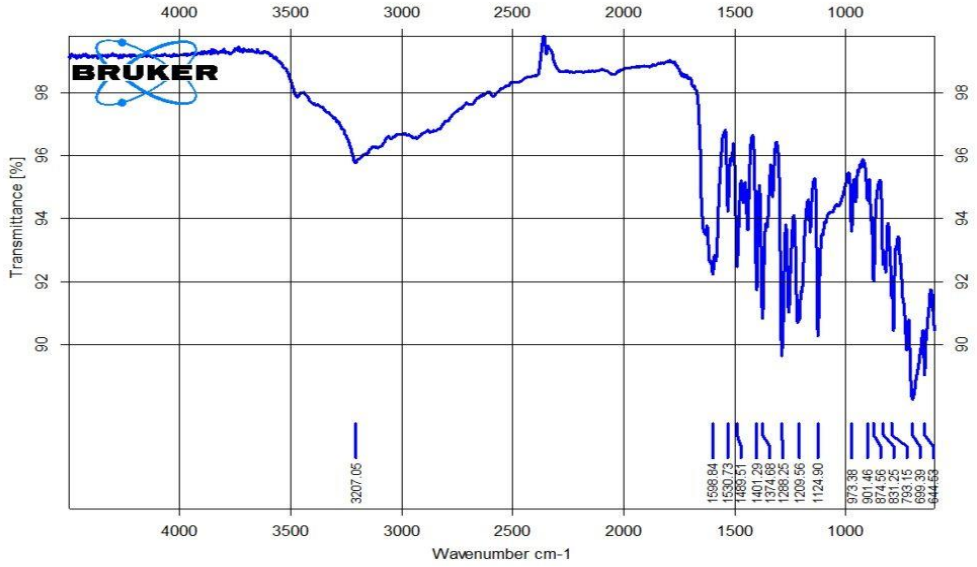

Figure 2: FTIR ZnO-NPs

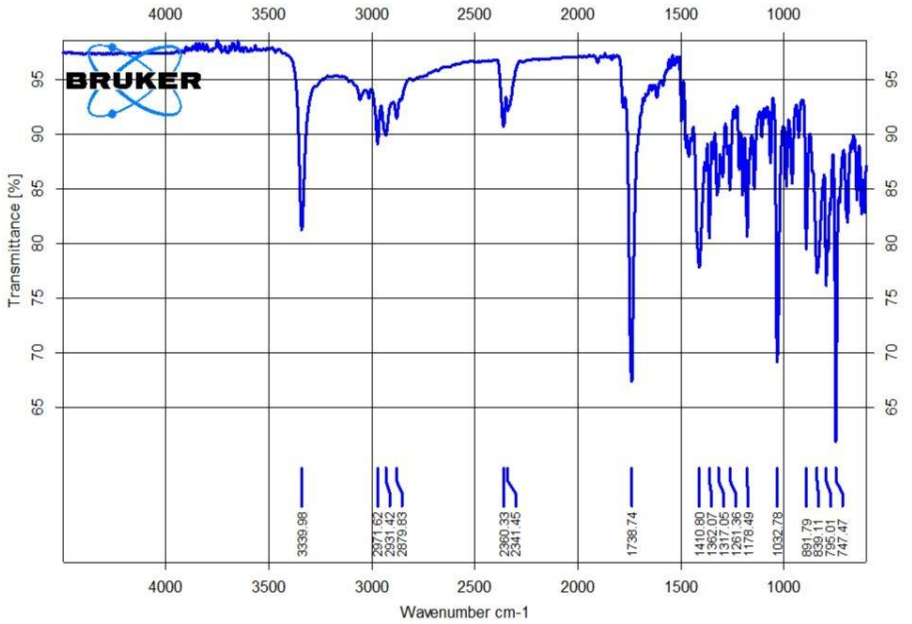

Figure 3: FTIR Etodolac

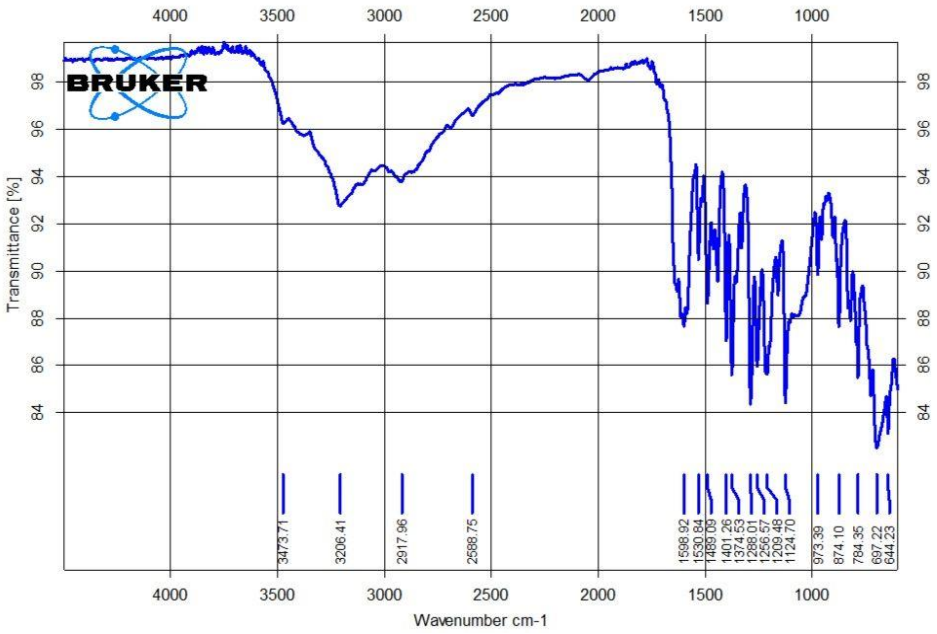

Figure 4: ZnO-NPs + Etodolac

2.4 The Scanning Electron Microscopy (SEM)

It studies the surface of the ZnO-NPs- Etodolac and the pure ZnO-NPs by using scanning electron microscopy to compare between them the results illustrated in Figure 5,6.

2.5 Drug Release%

An accurately weighed quantity of Etodolac conjugate nanoparticles was filed in capsules and placed in a beaker, which was immersed in 900 ml phosphate buffer having pH 7.4. The temperature of the media was maintained stable at 37 °C and stirred at a speed of 75 rpm. At specific time intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10 h). The collected samples were filtered and analyzed at 227 nm, using a UV-visible spectrophotometer against the phosphate buffer having pH 7.4 as a blank.

The equation 1 used to calculate the release percentage.

$$\text{Release\%} = \frac{Ct}{CT} \times 100 \text{ -------1}$$

3.Results and Discussion

3.1 The Fourier Infrared Spectroscopy (FTIR)

The Table 2, 3 and 4 explain the FTIR spectrum for Etodolac, ZnO-NPs- Etodolac and the pure ZnO-NPs

Table 2: FTIR Spectrum for Etodolac

Herbicides	**υC-H Aromatic**	**C-O**	**υC=O Acid**	**υC=C Aromatic**	**δC-H Aromatic**	**δN-H**
Etodolac	2879	1261	1738	1410	747	3339

Table 3: FTIR Spectrum for ZnO

Herbicides	**υ (Zn-O)**
ZnO	644

Table 4: FTIR Spectrum for ZnO-NPs

Herbicides	**υC-H Aromatic**	**υ (C=C) Aromatic**	**N-H**	**δ(C-H) Aromatic**	**υ (Zn-O)**
ETO-ZNO	**2917**	**1401**	**3473**	**784**	**644**

The etodolac- ZnO-NPs show new bands that indicate to successful process of inserting the Etodolac between the ZnO nanoparticle's layers.

The broad band at 3443cm-1 refer to starching vibration for the (OH) group. The υC=O disappears in the etodolac-ZnO-NPs and a new band at 644 cm-1 belonging to the Zn-O bond appears ((Ibrahim, Nada and Kamal, 2005), (Cornejo *et al.*, 2000)).

3.2 The Scanning Electron Microscopy (SEM)

Figures 5 and 6 show the difference between the size and the shape of particles for pure Zn-NPs and ZnO NPs-Etodolac that proved the load of Etodolac on ZnO-NPs

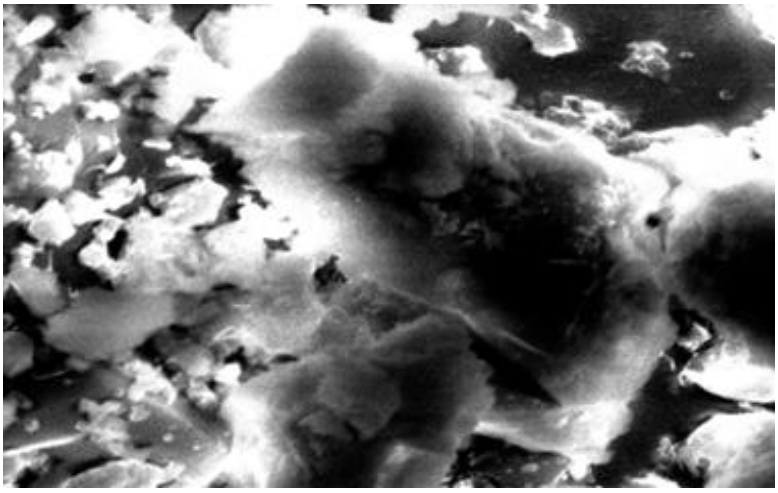

Figure 5: SEM for ZnO- NPs

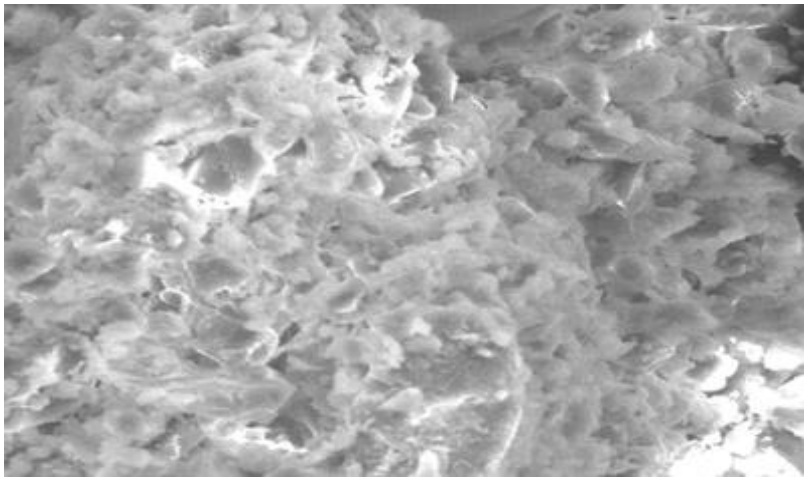

Figure 6: SEM for ZnO + Etodolac

Figure 5 observes the electron microscope images of zinc oxide before insertion, the presence of plate-like structures with low porosity, shapes, and sizes are unknown in the electron microscope images of the hybrid nanocomposite. Figure 6 shows the presence of structures with high porosity between the layers as a result of the attraction between Etodolac and the surface of the zinc oxide nanoparticles, which was shown by previous studies (Rosa *et al.*, 2013). The insertion of the compound into the zinc oxide changes from an irregular shape to nanostructured plates.

3.3 Drug Release

The drug release in Table 5 shows that the highest percent 98% at 50 min.

Table 5: The Etodolac Release with Time

Time / min	Drug Release%
5	15.3
10	24.5
15	33.7
20	42.2
25	55.3
30	62.1
35	73.3
40	82.1
45	90.5
50	98.7
55	98.7
60	98.7

4. Conclusion

ZnO and Etodolac-loaded ZnO nanoparticles were successfully characterized by FTIR and SEM. The analysis confirmed the loading of Etodolac onto the ZnO NP surface. The highest percentage of drug release occurred within 50 minutes. Notably, the incorporation of Etodolac into the zinc oxide structure resulted in a morphological transformation, changing from an irregular shape to nanostructured plates. Furthermore, the disappearance of the υC=O peak in the FTIR spectrum of Etodolac-loaded ZnO NPs provides compelling evidence for the successful formation of these nanocomposites

References

Biswal, M. S. (2020) ‘Studies on the Development of New Analytical Methods and Validation of Some Potential Drug Candidates Using Modern Analytical Tools’. Visakhapatnam.

Brocks, D. R. and Jamali, F. (1994) ‘Etodolac clinical pharmacokineticsBrocks, D.R. and Jamali, F. (1994) “Etodolac clinical pharmacokinetics”, Clinical pharmacokinetics, 26(4), pp. 259–274.’, *Clinical pharmacokinetics*. Springer, 26(4), pp. 259–274.

Çırpanlı, Y. *et al.* (2009) ‘Etodolac Loaded Poly Lactide-Co-Glycolide Nanoparticles: Formulation and In Vitro Characterization’, *Hacettepe University Journal of the Faculty of Pharmacy*. Hacettepe University, (2), pp. 105–114.

Cornejo, J. *et al.* (2000) ‘Structural changes in phenol-intercalulated hydrotalcite caused by heating’, *Clay minerals*. Cambridge University Press, 35(5), pp. 771–779.

Haldorai, Y. and Shim, J.-J. (2014) ‘An efficient removal of methyl orange dye from aqueous solution by adsorption onto chitosan/MgO composite: A novel reusable adsorbent’, *Applied surface science*. Elsevier, 292, pp. 447–453.

Ibrahim, M., Nada, A. and Kamal, D. E. (2005) ‘Density functional theory and FTIR spectroscopic study of carboxyl group’. CSIR.

Jain, N. K. (1997) *Controlled and novel drug delivery*. CBS publishers & distributors New Delhi.

Kirkby, N. S. *et al.* (2013) ‘LC-MS/MS confirms that COX-1 drives vascular prostacyclin whilst gene expression pattern reveals non-vascular sites of COX-2 expression’, *PloS one*. Public Library of Science San Francisco, USA, 8(7), p. e69524.

Mohanraj, V. J. and Chen, Y. (2006) ‘Nanoparticles-a review’, *Tropical journal of pharmaceutical research*, 5(1), pp. 561–573.

Rosa, R. *et al.* (2013) ‘Microwave-assisted melt reaction method for the intercalation of carboxylic acid anions into layered double hydroxides’, *Journal of Microwave Power and Electromagnetic Energy*. Taylor & Francis, 47(1), pp. 12–23.

Seay, I. F. and Elim, H. I. (2019) ‘The observation of fast, long term, and stable performance of toxic absorption in herbal blessing product based on galoba maluku (Zingiberaceae Fruits)’, *Science*, 2(2), pp. 122–127.

Soenen, S. J. *et al.* (2015) ‘(Intra) cellular stability of inorganic nanoparticles: effects on cytotoxicity, particle functionality, and biomedical applications’, *Chemical reviews*. ACS Publications, 115(5), pp. 2109–2135.

Sutapa, I. W. *et al.* (2018) ‘Synthesis and structural profile analysis of the MgO nanoparticles produced through the sol-gel method followed by annealing process’, *Oriental Journal of Chemistry*. Oriental Scientific Publishing Company, 34(2), p. 1016.