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E-B Environment - Behaviour Proceedings Journal

ICWEP2022

https://icwep.uitm.edu.my/index.php
International Conference on Wood and Eco-Products 2022
Best Western Hotel iCity, Shah Alam, Selangor, Malaysia 15-16 Nov 2022
Organiser: Faculty of Applied Sciences, Universiti Teknologi MARA (UiTM), Shah Alam Malaysia & Research Nexus UiTM,, Office of Deputy Vice-Chancellor (Research & Innovation)

e-IPH e-International Publishing House Ltd., United Kingdom

Kinetic Study of Natural Anticancer Drug (Zerumbone) Release from Zeolite Y-Gelatin Hybrid for Oral Controlled Delivery

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Abstract
A hybrid of zeolite Y-gelatin film as an oral dosage form for the natural anticancer drug was achieved by homogenously incorporating the drug-loaded zeolite Y into the gelatin solution. Drug ability was analyzed using computational and experimental approaches, drug encapsulation efficiency via the BET method, and possible interactions by FTIR analyses. Zerumbone released was done in both pH 1.2 and pH 7.4 mimicking the human gastrointestinal tract conditions for 24 hrs and subjected to kinetics study via suitable mathematical models to determine what governs the drug release with the results indicating that a sustained delivery of once-daily oral dosage form could be achieved.

Keywords: Kinetic study; oral controlled release; zeolite Y; zerumbone

DOI: https://doi.org/10.21834/e-bpj.v9iSI17.5441

1.0 Introduction

Cervical cancer is one of the most common cancers among Malaysian women (MNCRR, 2003). Despite being potentially preventable, this disease is known as a 'silent killer' as most women do not realize they have the disease earlier as the symptoms mostly tend to appear during later stages (WHO, 2017). Moreover, the death rate is more than two times higher than in other Asian and Western countries even with the practice of screening programs and immunizations, triggers worry among health and medical practitioners (Zaridah, 2014; Aljunid et al., 2010; Shanthi et al., 2012). Treatments for cervical cancer is highly known for the use of powerful synthetic cytotoxic chemotherapy drugs to kill fast-growing cancerous cell (Chabner et al., 2005) is an aggressive form of chemical drug therapy had cause endless serious sides effects that can severely impact the quality of life (Weaver, 2014). Therefore, notable opportunities for new cancer drug discovery had undergone a significant change over the last decade (Workman, 2005; Singh et al., 2016) leading to the potential of natural products (Rayan et al., 2017) as anticancer drugs with the first anticancer drug was recognized in the 1950s by U.S National Cancer Institute (NCI, 1950).

Most chemo drugs can be released intravenously (IV) or orally, except for cervical cancer treatment that only necessitates IVs, which is quite challenging and burdensome for cancer patients as it can only be done at cancer clinics or appointed hospitals. This method required patients to sit for hours to finish the treatment is unacceptable (WHO, 2017), hence modern-day chemo drug delivery should utilize the controlled release technology via the oral route for drug administration (Wen et al., 2010; Nichols et al., 2014). It greatly offers advantages including prolonged drug delivery within the therapeutic range, single dosage daily, self-administer scheduled dose at home,

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DOI: https://doi.org/10.21834/e-bpj.v8iSI17.5441

undisturbed patient's daily routines as well as reducing the number of resources needed for the care services relating to chemotherapy, therefore much more convenient, economical and manageable (Zaridah, 2014).

2.0 Literature Review

Plant-derived anticancer agents have dramatically changed conventional chemotherapy treatment as there are much simpler, safer, eco-friendly, and low cost of production with faster and less toxic sides effect (Iqbal et al., 2017). Zerumbone (ZER) is a bioactive compound isolated from the rhizome of ginger from the Zingiberaceae family and can be found abundantly in rhizomes of *Zingiber Zerumbet (L) Smith* and known as *lempoyang* in Malaysia (Mukarami et al., 2002). Anticancer properties of zerumbone have been reported in various studies at different concentrations and doses, both in vitro and in vivo. Studies also show that zerumbone exhibits antiproliferative properties, which can retard the spread of several malignant cans into surrounding tissues with minimal effect on normal cells (Rahman et al., 2014).

Drug carriers must be inert and compatible when exposed to the living tissue and/or bodily fluids and formulations designed for prolonged delivery required high initial drug loading. Among all biopolymers, gelatin can be used for sustained drug delivery. Due to its biocompatibility and biodegradability, it can easily be excreted through the usual metabolic process by the body (Zhang et al., 2013). To accomplish prolonged (extended) release, the formulation requires enormous initial drug loading. As a single component, gelatin can exhibit undesirable mechanical properties and does not have the advantages of drug encapsulation (Ribeiro et al., 2017).

Therefore, zeolite Y a porous aluminosilicate with the advantages of small size and large surface area per unit volume attained the capability of the highest drug loading and drug entrapment (Salazar et al., 2015) is paired together with gelatin to improve their performance contribute to the development of new hybrid materials with combined properties of two or more materials that appear greater to the individual material systems.

3.0 Methodology

3.1 Preparation of OIH Film

ZER crystals obtained from the rhizomes of Zingiber Zerumbet (L) Smith were isolated and purified according to methods in earlier studies (Abdul et al., 2008) was first loaded into porous zeolite Y with continuous stirring and dried at room temperature. Then, 10 grams of GEL powder was soaked in 50 ml of deionized water and heated to 70 ºC with the addition of glycerin (5 grams). The drug-loaded zeolite Y prepared earlier was mixed into a GEL solution and homogenously stirred before casting into a thin film. The hybrid solution was left to cool in the refrigerator and cut into the desired dimension before cross-linked with glutaraldehyde (GTA) at 0.2 v/v% into previously cooled sunflower oil (10 ºC for 24 hrs). The cross-linked sample was freed from oil through repeated washing with isopropyl alcohol, and this experiment is repeated for 5,10, and 15 v/v% of ZER concentrations. All samples were kept in a desiccator until further use.

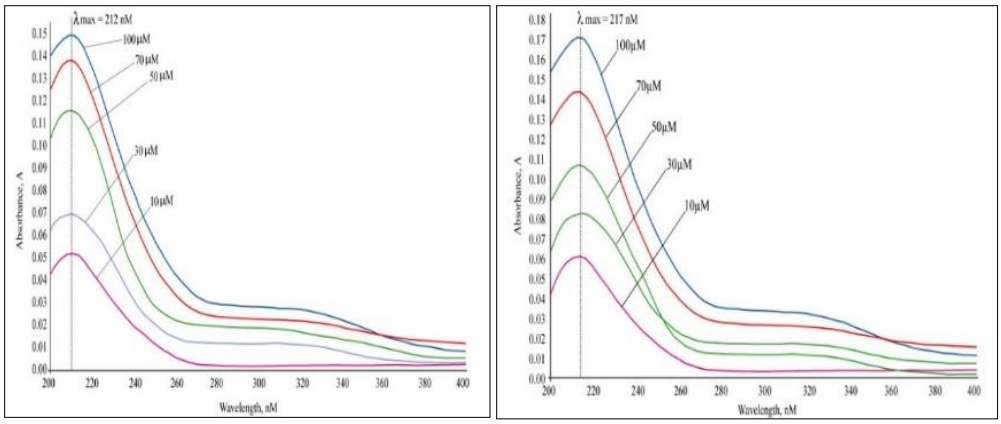
3.2 Characterizations

Samples were subjected to various testing methods such as drug-ability analysis via computational and experimental methods. Computational analysis was achieved by using MARVIN BEAN software and experimental methods via the UV-VIS method. Porosity analysis was done via BET analyzer model Quantachrome Autosorb Automated Gas Sorption and FTIR analysis was carried out on NICOLET 6700 model. The drug release analysis was measured at λ= 212 nm at pH 1.2 and λ= 217 nm at pH 7.4 using a UV-Vis spectrophotometer model PERKIN ELMER UV/VIS Lambda 20. The experiments were conducted in triplicate and the absorption values, *A*, were averaged. Kinetics study was done by using several mathematical models representing dissolution drug profile as a function of time-related to the amount of drug dissolved from the dosage form, which are zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas kinetics model with the correlation coefficient, r^2 value calculated from each kinetic model were used as an indicator of the best fit model, and the drug release kinetic parameter namely diffusion coefficient, *n* calculated from the slope of Korsmeyer - Peppas models describes the mechanism of drug released (Thakur et al., 2013).

4.0 Results and Discussions

4.1 Physicochemical Properties of ZER

The software analysis described ZER as an unsaturated cyclic aliphatic compound with a chemical formula of $C_{15}H_{22}O$, 218.16 Da of molecular weight with an estimated ring size of 11Å, possess logP= 5.34 and logD= 4.72 (logP≠logD) and having oxygen as a polar atom with PSA value of 17 Å has categorized ZER as a small molecular weight drug (MW<500 Da) suitable for the oral route as main delivery path according to Biopharmaceutics Classification System (BCS). ZER with the highest absorbance at λ_{max} = 250 nm shifted to 212 nm and 217 nm concerning pH 1.2 and pH 7.4 due to the effect of dissolved ZER chromophore in phosphate buffer saline solution. A linear relationship with the two variables was found for correlation coefficient, r^2 values of 0.882 and 0.907 for pH 1.2 and pH 7.4 respectively, assuring ZER solubility and stability in human GIT conditions.



(a) (b)

Fig 1: UV-Vis spectra of zerumbone absorption with λ_{max} at (a) pH 1.2 and (b) pH 7.4

4.*2 Incorporation of ZER into Zeolite Y*

The pore volume of zeolite Y before and after ZER loading was tabulated in Table 1, and the mass of ZER incorporated into zeolite Y was determined respectively by Equations 1 and 2. From the calculation obtained in Table 1, 100 % of ZER was found to incorporate and scattered within the pores, with more than 50 % found residing near the pore opening.

$$m = \rho v \quad (1)$$

m = Mass of ZER after incorporated into zeolite Y
ρ = Density of ZER (0.888 g/cm^3)
V = Volume of zeolite Y pores that have been incorporated by ZER

$$Encapsulation\ efficiency = \frac{M2}{M1} \text{ x } 100 \quad (2)$$

M_1= Initial mass of ZER
M_2= Mass of ZER loaded in zeolite Y pores

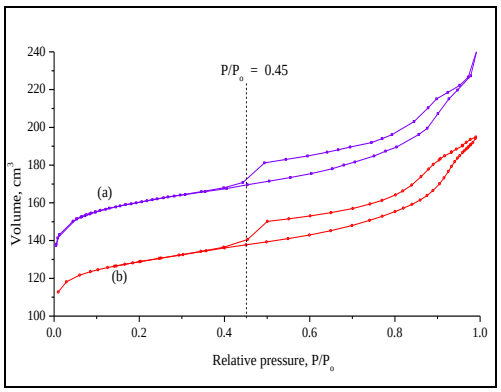


Fig 1: Plot of hysteresis curves of (a) zeolite Y and (b) ZER-loaded zeolite Y at a concentration of 100 µm

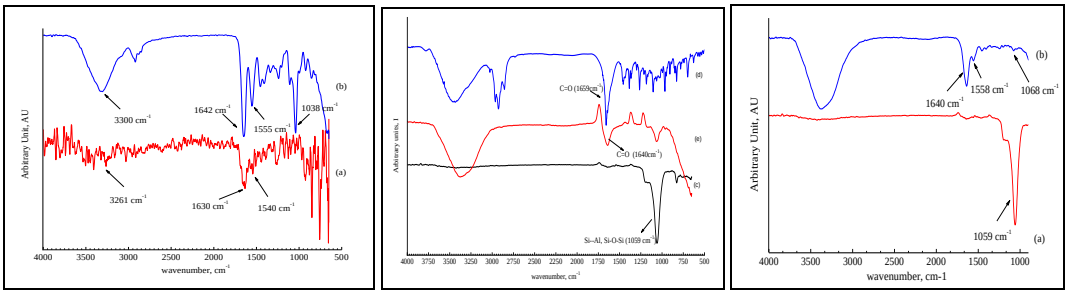
Table 1: Pore size distribution and encapsulation efficiency of ZER

Concentration µM	M_1 g	Pore distribution Å	V_b cm^3	V_a cm^3	$V_{zerumbone}$ cm^3	M_2 G	EE %
100	0.0109	14.55	0.141	0.147	0.006	0.006	51.4
		38.80	0.111	0.114	0.004	0.003	28.4
		156.60	0.061	0.063	0.003	0.002	20.2
					Total encapsulation		100

4.3 Fourier Transform Infra-Red Analysis

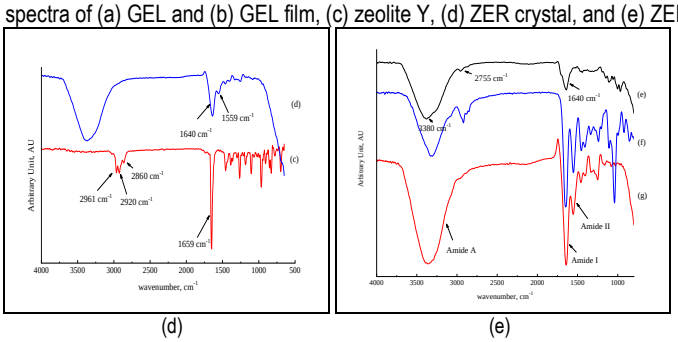
The absorption bands of pure GEL in the infrared spectra were situated in the amide band regions with a broad peak at 3261cm^{-1} signifies Amide A (-OH and -NH groups), C=O stretching (Amide I) at 1630 cm^{-1}, N-H bending (Amide II) at 1540 cm^{-1}, with several peaks arise from 1460 -1200 cm^{-1} related to C-H deformation (Amide III) (Figure 3a). Zeolite Y (Figure 3c) provides information with a strong peak at 1059 cm^{-1} that corresponds to Si-O-Al and Si-O-Si bonds (Dat, 2012), with ZER-zeolite Y (Figure 3e) showing a prominent

peak ~1640 cm^{-1} assigned to the carbonyl group (C=O) of ZER. GTA (Figure 4e) presented a broad peak at 3380 cm^{-1} due to the stretching vibration of water, CH_2 vibration of aldehyde close to 2755 cm^{-1}, C=O at 1640 cm^{-1} (Migneault et al., 2004). It was observed that the intensity of the hybrid film increased after cross-linked at 1639 cm^{-1} (Figure 4g) mainly contributed by the formation of the imine linkages (C=N) from GEL-GTA cross-linking chain overlapped with the C=O stretching from the GEL film.



(a) (b) (c)

Fig 3: FTIR spectra of (a) GEL and (b) GEL film, (c) zeolite Y, (d) ZER crystal, and (e) ZER-zeolite Y

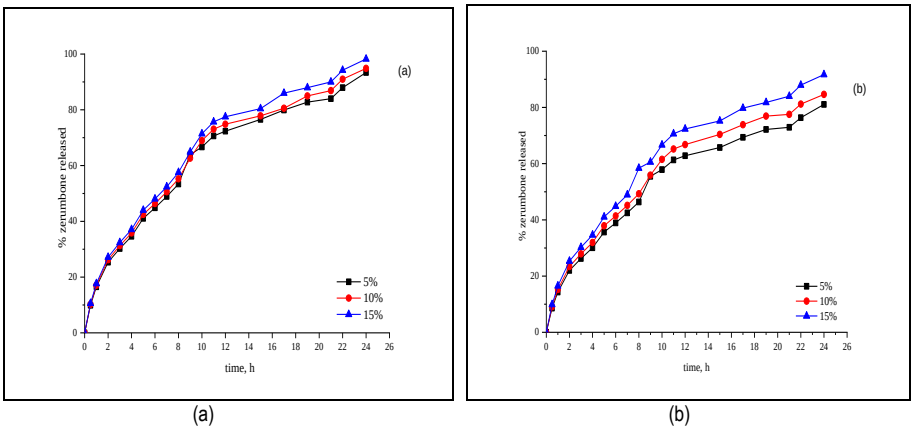


(d) (e)

Fig 4: FTIR spectra of (a) zeolite Y, (b) zeolite Y-GEL, (c) ZER crystal, and (d) ZER-GEL, (e) GTA, (f) ZER-ZEO Y/GEL, and (g) cross-linked ZER-ZEO Y/GEL film

4.5 ZER Release from OIH Film

The measured percentage of drug release in Figure 5 shows a significant increase in ZER release with increasing drug concentrations, interestingly, more than 90% of ZER is released from the composites at pH 1.2 within 24 hours as compared to pH 7.4. This suggests that the ionic interaction of the hybrid films easily broken at acidic pH, leading to more ZER being released rapidly at the upper GIT (stomach area) as compared to the small intestines. However, a similar release pattern with the first initial burst release followed by slower release within 8 to 10 hours and fast release as reaching 24 hours of drug delivery, subjected to both pH conditions (Figure 5). A burst release is mainly due to the position of drug molecules that are hat held just beneath the matrix surface contributes to the burst effect, which is a common effect for a matrix-type system (Santoro et al., 2014).



(a) (b)

Fig 5: Cumulative percentage of drug release at 5-15% ZER loadings at (a) pH 1.2 and (b) pH 7.4 from cross-linked zeolite Y-GEL composite

4.6 Kinetics and Mechanism of ZER Release

To investigate the drug release kinetics, release data were plotted into various kinetics models as shown in Figure 7, where models that obtained the highest correlation coefficient (r^2) value indicate the best fit model. ZER release of a zero-order kinetics model defines the process of constant drug release with calculated r^2 = 0.891-.0.892 for pH 1.2 and r^2= 0.8860-0.8929 for pH 7.4. The first order model (i.e., the rate is directly proportional to the concentration of the drug undergoing reaction i.e., the greater the concentration faster the

reaction) exhibits r^2=0.9291-0.9739 and r^2=0.9755-0.9836, ZER release from Higuchi models involves both dissolution and diffusion shows r^2= 0.9836-0.9849 and r^2=0.9836-0.9853, Hixson-Crowell cube root law describes ZER drug release from systems with a change in surface area and diameter with r^2=0.9724-0.9784 and r^2=0.9565-0.9722, while Korsmeyer-Peppas model presents r^2= 0.995-0.996 and r^2= 0.993-0.995 at pH 1.2 and pH 7.4 respectively. Most kinetic models (except the zero-order model) present r^2 values closely approaching the trendline, but ZER release is best fitted into the Korsmeyer-Peppas model which described the drug diffusion from a polymeric system. To determine which type of diffusion it follows, the *n* value obtained from the slope of the graph is used to characterize different release mechanisms as tabulated in Table 2, where the release exponent is 0.5 < n < 1, which indicates an anomalous diffusion.

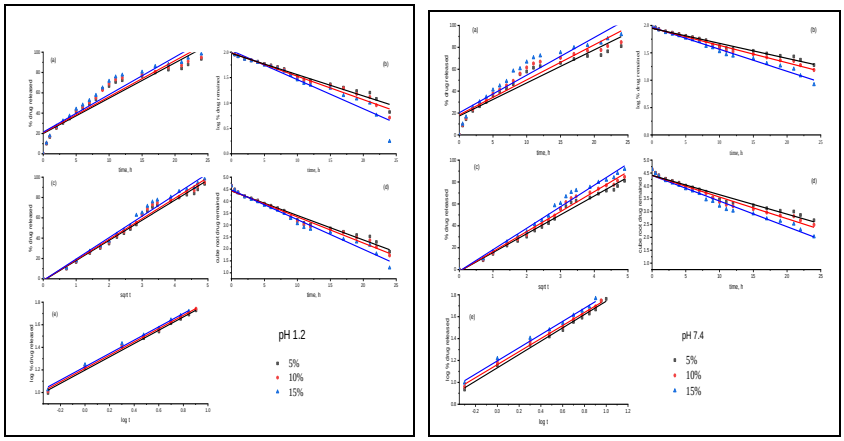


Fig 7: ZER release from (a) zero order, (b) first order, (c) Higuchi, (d) Hixson-Crowell, and (e) Korsmeyer Peppas kinetic models from both pH 1.2 and pH 7.4 at ZER concentration 5-15v/v%

5.0 Conclusion and Recommendations

From the data obtained, we concluded that sustained oral delivery of a natural anticancer drug (ZER) for 24 hours was successfully achieved from the zeolite Y-GEL hybrid system. Due to the high sensitivity of GEL towards the pH of GIT, cross-linking was introduced via GTA at a concentration of 0.2 v/v% for 24 hours of cross-linking time, representing the optimum condition for achieving 24 hours of drug delivery. The reinforced polymeric layer governed the diffusion of the drug from the hybrid system via swelling and the later erosion process will govern the remaining drug delivery demonstrates the possibility of oral natural chemotherapy drug delivery for cervical cancer treatments, with the aid of advanced materials developments in the drug delivery field based on hybrid materials. This study aims to introduce natural chemotherapy drugs with their potential advantages and benefits as compared to conventional chemotherapy drugs (and their side effects) for cervical cancer treatments. We also have made efforts in designing an innovative hybrid drug delivery system, as the search for a perfect drug delivery system is still a challenge.

6.0 Acknowledgements

The authors would like to express their gratitude to the Faculty of Applied Sciences, Universiti Teknologi MARA (UiTM) Shah Alam, Selangor Malaysia, for the facilities and guidance and their assistance as ReNeU, UiTM for the PYPB incentive.

7.0 Paper Contribution to Related Field of Study

The results presented in this study may find extensive usage in the growth of construction industries, either as a building material or limestone aggregate for road building, as ingredients of cement, or as a starting material for the preparation of a builder's lime. In the medical area, it can be used as an antacid or as a calcium supplement, as well as a filler in cosmetics preparation. Furthermore, it can be a disinfectant agent and pH corrector when added to the pool water.

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