Bahan Penghatar Obat Berbasis Zeolit Alam

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Grup Riset Kimia Analitik

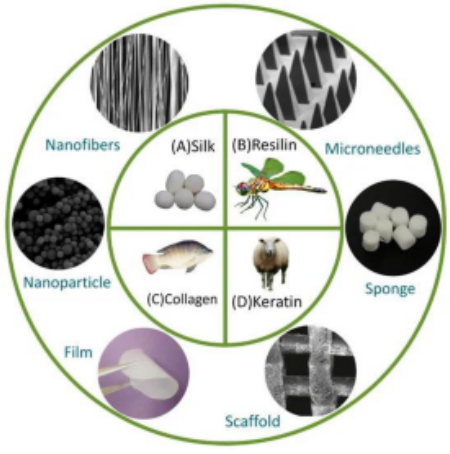
Penyisihan polutan
- Adsorpsi dengan IIP dll
- degradasi dengan nanokomposit
- adsorpsi dengan nanopartikel mag

Pengembangan teknik preparasi sampel

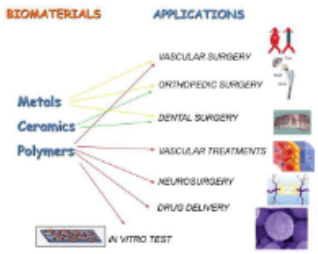
- mikroekstraksi (SPE, SDME, DLLME)
- ekstraksi dengan nanopartikel magnetic
- Estraksi dengan material polimer tercetak ion

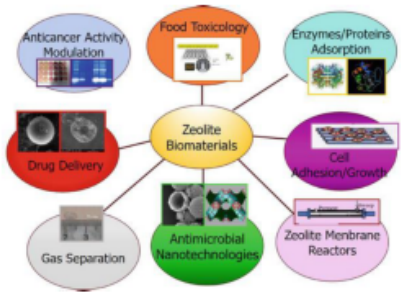
Biomaterial

Bahan penghantar obat berbasis material anorganik



Material penghatar obat berbasis zeolite alam

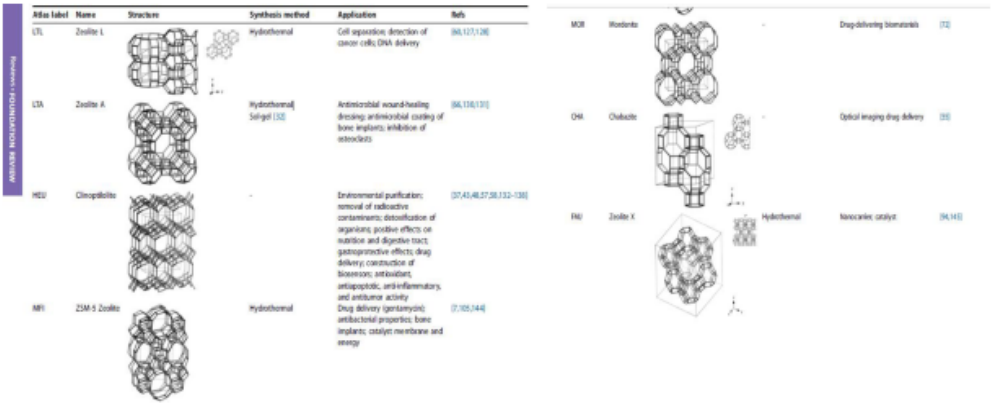




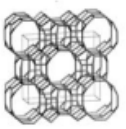
Zeolite any of a large group of minerals comprising hydrated aluminosilicates of sodium, potassium, calcium, and barium. They can be readily dehydrated and rehydrated, and are used as cation exchangers and molecular sieves.

Zeolite can be used as a platform for the delivery of various types of drug. However, because of the small size of the drugs, they can be easily released from the structure. Therefore, the zeolite pore size needs to be adjusted in terms of the desired drug [29]. Moreover, differences in hydrophilicity between zeolites and drugs can limit their loading capacity, although this can be overcome via surface modification of the zeolite [30,31]. Thus, the surface of a zeolite can be adjusted depending on the drug that needs to be delivered. Table 1 details examples of zeolite structures, properties, and applications in biomedical applications.

Examples of zeolites used in biomedical applications



Atlas label	Name	Structure	Synthesis method	Application	Refs
LTL	Zeolite L		Hydrothermal	Cell separation; detection of cancer cells; DNA delivery	[66,127,128]
LTA	Zeolite A		Hydrothermal[Sol-gel [32]	Antimicrobial wound-healing dressing; antimicrobial coating of bone implants; inhibition of osteoclasts	[66,130,131]
HEU	Clinoptilolite		-	Environmental purification; removal of radioactive contaminants; detoxification of organisms; positive effects on nutrition and digestive tract; gastroprotective effects; drug delivery; construction of biosensors; antioxidant, antiapoptotic, anti-inflammatory, and antitumor activity	[37,43,48,57,58,132–138]
MFI	ZSM-5 Zeolite		Hydrothermal	Drug delivery (gentamycin); antibacterial properties; bone implants; catalyst membrane and energy	[7,105,144]
MOR	Mordenite		-	Drug-delivering biomaterials	[72]
CHA	Chabazite		-	Optical imaging drug delivery	[33]
FAU	Zeolite X		Hydrothermal	Nanocarrier, catalyst	[94,145]



Mordenite

zeolite mineral with the chemical formula, (Ca, Na2 K2) Al2Si10O24.7H2O orthorhombic

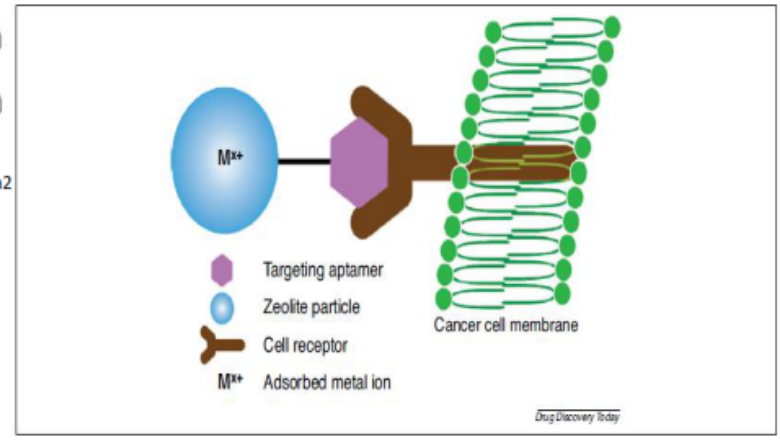
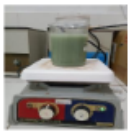


FIGURE 1

Bifunctional zeolites in targeted therapy and imaging. Reproduced, with permission, from [94].

Mordenite purification from natural zeolite

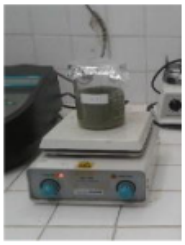
Natural zeolite was ground and sieved with a size of 100 mesh. Then the 200 g of zeolite was washed with 750 mL of RO water while stirring for 30 min at a temperature of 70 °C. Washing was carried out four times to remove impurities. Furthermore, natural zeolite that has been cleaned is dried in a heating oven to remove water. Moreover, purification of mordenite from natural zeolite was carried out in an alkaline way, namely washing natural zeolite with 3 M NaOH for 4 h while stirring. The natural zeolite was then filtered using filter paper Whatman 41 and cleaned using RO water until the pH was neutral. The natural zeolite was then dried at 300 °C in a muffle furnace for 3 h. The results obtained were then given the name Mor.



NaOH will cause the active site of the zeolite to be more open and can increase the adsorption capacity where Na+ ions play a role in dissolving Si to form a sodium silica zeolite structure that becomes more negatively

Synthesis of Cu(II)-Mor material

The synthesis was carried out using the method approach Khatamian et al., [23] with a bit of modification. Mor (0.5 g) was suspended in NaCl solution (5 mL, 3 M) and stirred for 24 h. Then, Mor was separated using centrifugation at 2000 rpm and then washed several times using RO water. Mor was then dried at 60 °C. Mor powder was then added to a solution of $Cu(CO_2CH_3)_2$ (25 mL, 1 M), stirred for 24 h, separated by centrifugation at 2000 rpm, washed with demineralized water and then dried at 60 °C. The sample was then named Cu-Mor.

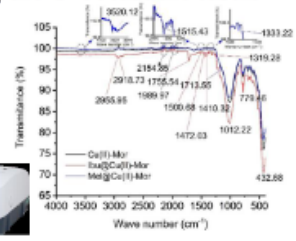


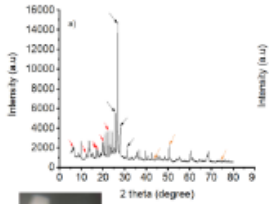
NaCl is used to increase the zeolite pore size so that the adsorption capacity increases.

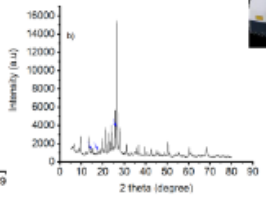
After being washed and then dried, the Mor powder was added to Cu(CH3-COO)2 solution. Coordination cations are necessary because it is impossible to make uniform and stable composites without coordination cations [23]. The addition of transition metal complexes in the zeolite cavity can promote high chemical, thermal and radiation stability and good activity and stability. This result is related to the output of research from Shebl et al. [48], where it can be seen that the encapsulation of Cu(II) with zeolite in the study showed that Cu(II)-zeolite has low toxicity and is biocompatible.

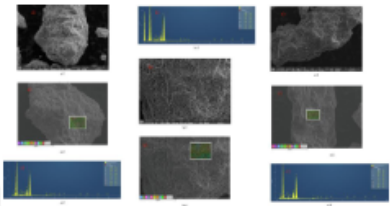
Characterization of drug delivery materials

Performing Physico-chemical characterization of Ibu@Cu(II)-Mor and Mel@Cu(II)-Mor materials and then characterized using XRD (Shimadzu XRD 7000 diffractometer (Shimadzu, Japan), FTIR (Perkin Elmer, with attenuated total reflectance method at a resolution of 4 cm^{-1} in the range of 400 cm^{-1}–4000 cm^{-1}, scan 16 times) and FESEM-EDS (Thermo Scientific Quatro S).



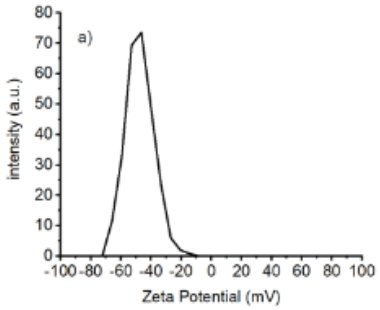


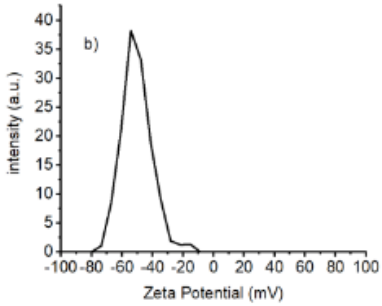




Zeta potential measurement

The dispersion stability of the drug-delivery material was studied using zeta potential Horiba SZ-100, dispersant aquadest, Size range −200 ± 200 mV. Ibu@Cu(II)-Mor or Mel@Cu(II)-Mor was crushed in RO water with a crusher before measurement.





it can be seen that the zeta potential of Ibu@Cu(II)-Mor and Mel@Cu (II)-Mor shows a considerable zeta potential value (negative value) which is -53.69 ± 0.3 mV and -46.51 ± 0.2 mV, respectively. It is known that the Zeta potential must have a minimum value of -30 mV before it is considered a drug delivery material that has good nanodispersion stabilization

Loading ibuprofen or meloxicam on Cu(II)-Mor

1000 mg of Cu(II)-Mor was added to 75 mL of a methanol solution containing 600 mg of ibuprofen or meloxicam. Then the solution was stirred for 24 h at room temperature. After the stirring process, the drug delivery sample was filtered and dried in an oven at 35 °C for 2 h. After that, the drug sample was kept in a desiccator until further processing. Meanwhile, the filtrate was measured at 200 nm for ibuprofen and 216 nm for meloxicam. [24]. The percentage of drug loading content (DLC, %) and percentage of entrapment efficiency content (EEC, %) is still determined through Equations (1) and (2), respectively [22].

$$\text{Drug loading } (\%) = \frac{\text{Weight of drug in Cu(II)} - \text{Mor}}{\text{Weight of Cu(II)} - \text{Mor}} \times 100 \quad (1)$$

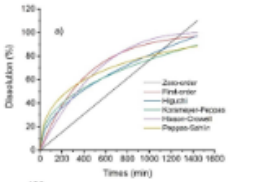
$$\text{Entrapment efficiency } (\%) = \frac{\text{Weight of drug in Cu(II)} - \text{Mor}}{\text{Weight of drug fed initially}} \times 100$$

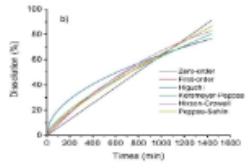
Drug carrier	Drug sample	Drug loading (%)	Entrapment Efficiency (%)
Cu(II)-Mor	Ibuprofen	54.74	91.24
	Meloxicam	54.40	54.40

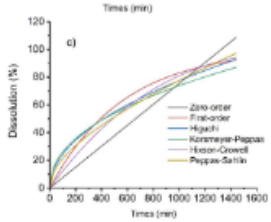
Drug release

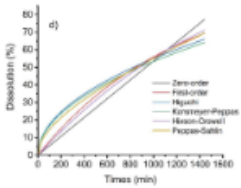
Samples of Mel@Cu(II)-Mor or Ibu@Cu(II)-Mor were each put into 50 mL of pH acid (pH 4), neutral (pH 7) and base (pH 9) buffer solution. Then the solution was spun for 24 h. Then the sample solution was taken as much as 5 mL at certain time intervals, then centrifuged at 1500 rpm for 5 min, filtered and then measured at a particular wavelength using UV–Vis at a wavelength of 200 nm for ibuprofen and 216 nm for meloxicam. At the same time, the sample solution was added 5 mL of RO water again so that the sample volume remained 50 mL. After a specific desorption time, there is no change in the concentration of meloxicam or ibuprofen in the sample solution. It is assumed that the maximum drug release has been achieved.

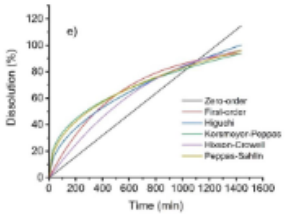
The linear standard curve of this studies of ibuprofen is A = 0.0023.C + 0.014 with R^2 = 0.999 and the linear standard curve of this



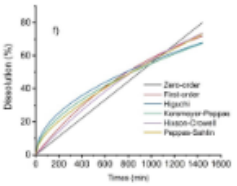








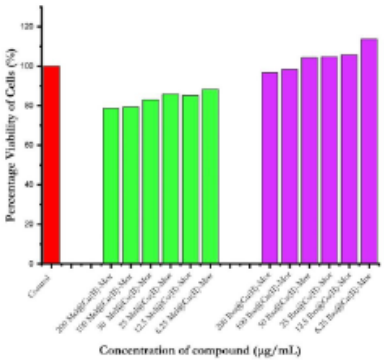
Drug carrier	Dissolution (%)		
	pH 4	pH 7	pH 9
Ibu@Cu(II)-Mor	72.46	90.98	86.03
Mel@Cu(II)-Mor	68.67	93.17	69.23



No	Indicator	Zero Order	First Order	Higuchi	Hixson–Crowell	Korsmeyer-Peppas	Peppas-Sahlin
Ibuprofen released from Cu(II)-Mor at pH 4							
1	R^2 adjusted	0.9468	0.9595	0.9007	0.9783	0.9634	0.9739
2	SS	265.3021	201.9019	495.0417	108.0163	182.2190	129.9816
3	AIC	41.0661	39.1545	45.4325	34.7760	40.4365	40.0717
Ibuprofen released from Cu(II)-Mor at pH 7							
1	R^2 adjusted	0.7574	0.8578	0.9028	0.8907	0.8763	0.9169
2	SS	1235.8228	724.2247	495.1717	556.6872	629.8509	423.4408
3	AIC	51.8364	48.0957	45.4343	46.2540	49.1184	48.3389
Ibuprofen released from Cu(II)-Mor at pH 9							
1	R^2 adjusted	0.0301	0.8495	0.8718	0.7281	0.9176	0.9664
2	SS	3248.2368	504.1794	429.2850	910.7517	276.0508	112.3752
3	AIC	58.6011	45.5605	44.4348	49.6999	43.3441	39.0529
Meloxicam released from Cu(II)-Mor at pH 4							
1	R^2 adjusted	0.8195	0.9364	0.9482	0.9143	0.9444	0.9648
2	SS	471.6928	166.2238	135.4783	223.8870	145.4310	91.8887
3	AIC	45.0943	37.7933	36.3617	39.8780	38.8579	37.6440
Meloxicam released from Cu(II)-Mor at pH 7							
1	R^2 adjusted	0.3480	0.8883	0.9505	0.8029	0.9722	0.9750
2	SS	2416.8614	414.0847	183.5956	730.7676	103.0999	92.8200
3	AIC	56.5316	44.1825	38.4892	48.1587	36.4499	37.7146
Meloxicam released from Cu(II)-Mor at pH 9							
1	R^2 adjusted	0.8765	0.9565	0.9406	0.9471	0.9530	0.9720
2	SS	376.8597	132.7537	181.3613	161.3830	143.4185	85.4438
3	AIC	43.5231	36.2195	38.4034	37.5865	38.7604	37.1350

showed that the dissolution of ibuprofen or meloxicam from Cu(II)-Mor at pH 7 followed the Peppas-Sahlin kinetic mechanism. The Peppas-Sahlin method was chosen because it has the highest adjusted R2 value, the lowest sum of squares (SS), and the Akaike information criterion (AIC) (Zhang et al., 2010). Based on Figure 7 and Table 4, this result indicates that the ibuprofen or meloxicam transport release from Cu(II)-Mor was controlled by Fickian diffusion and case II relaxations (Unagolla & Jayasuriya, 2018). Peppas – Sahlin model is the second term of Case-II relaxational contribution with m is pure Fickian diffusion exponent for any geometric shape of material drug delivery which shows controlled release (Peppas & Sahlin, 1989).

Drug material cytotoxicity test



The MTT assay test is a quantitative colorimetric test that can measure cell viability, proliferation and activity (Kumar et al., 2018). The cytotoxicity Ibu@Cu(II)-Mor, dan Mel@Cu(II)-Mor on Vero cells was evaluated by MTT assay. Figure 8 shows the viability of the vero cell exposed to 6.25 – 200 µg/mL of Ibu@Cu(II)-Mor or Mel@Cu(II)-Mor. Cytotoxicity tests were carried out to evaluate the biocompatibility of Ibu@Cu(II)-Mor and Mel@Cu(II)-Mor. A compound is said to have low cytotoxicity if it has a cell viability value of more than 80% (Fahmi et al., 2018). It is known that mordenite can be used as a drug delivery system (Hao et al., 2021). The graph (Figure 8) shows that Mel@Cu(II)-Mor has a good value of Vero cell viability at a concentration of 50 g/mL. While Ibu@Cu(II)-Mor showed Vero cell viability of more than 90%. This result showed that Cu(II)-Mor had better potential to use as a safe drug delivery agent because it showed good biocompatibility properties.