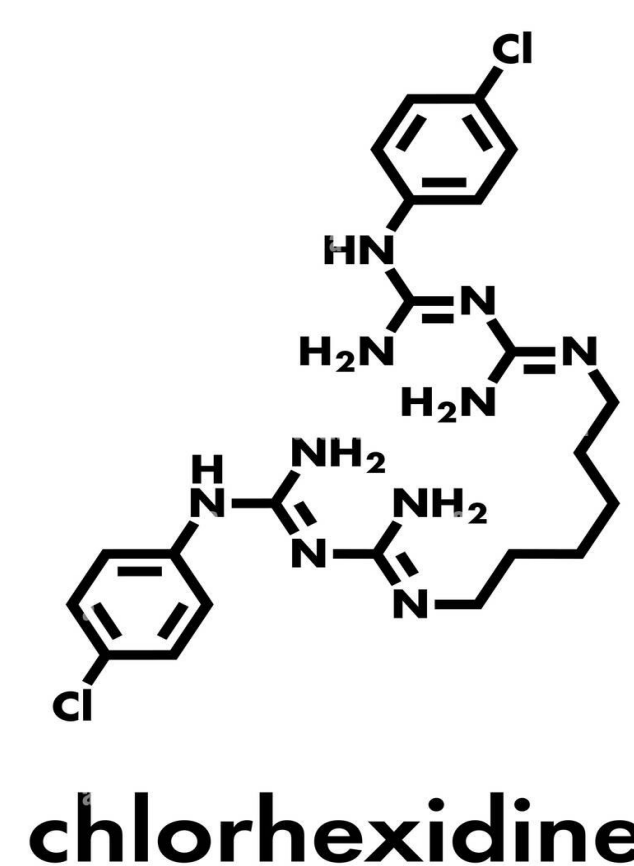


Introduction

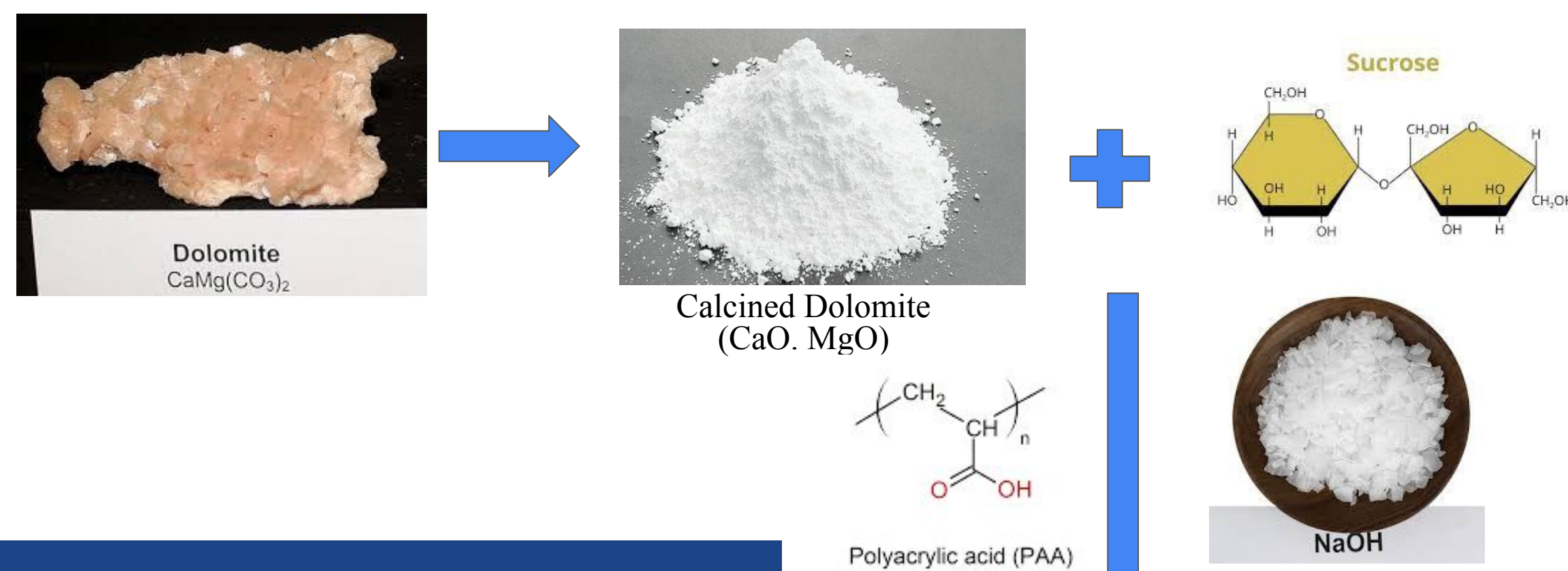
- Dolomite ($\text{CaMg}(\text{CO}_3)_2$) is a naturally available carbonate mineral rich in calcium (Ca) and magnesium (Mg) sources.
- It is a low-cost, naturally abundant, and environmentally friendly material that has been identified as a promising precursor for biomedical applications.
- Calcium carbonate nanoparticles (CaCO_3NPs) were synthesized by an *in situ* polymerization process, which involved the polymerization of MMA and the nucleation of CaCO_3 from natural dolomite.
- Chlorhexidine (CHX), an antimicrobial and antiplaque agent, was incorporated into synthesized CaCO_3NPs by using two drug-loading techniques: incipient wetness impregnation (IWI) and absorption equilibrium (AE) methods.
- In vitro drug release studies were conducted by the dialysis method in both acidic (pH 5.5) and neutral (pH 7.4) medium to study their drug releasing and their kinetics models.



Objective: This study aims to develop the most effective CHX drug-loaded calcium carbonate nanoparticles (CaCO_3NPs) for controlled drug delivery. For that, the natural dolomite is used to synthesize CaCO_3NPs via an *in situ* polymerization process, optimize CHX drug loading using two techniques (incipient wetness impregnation (IWI) and absorption equilibrium (AE)), and investigate their *in vitro* drug release profiles under different pH conditions and further analysis based on drug release kinetic models.

Methodology

CaCO_3NPs synthesis- *in situ* polymerization process



Drug Loading experiments

1. Absorption Equilibrium (AE)

Adding 125 mg of CaCO_3NPs to a 2% CHX solution in IPA by 1:1 ratio

Stirring for 24 hours

Measuring the absorbance of supernatant at 260 nm

2. Incipient Wetness impregnation (IWI)

Adding dropwise 2% CHX/ IPA solution to 125 mg of CaCO_3NPs

Maintaining 37 °C for dry particles

CHX encapsulation efficiency (EE)

$$EE = \{(\text{Initial CHX concentration} - \text{free CHX concentration}) / (\text{Initial CHX concentration})\} \times 100$$

Mathematical models for drug release

01. Zero-order model ————— $Q_t = Q_0 + K_0 t$

Q_t : Amount of drug released at time t

Q_0 : Initial amount of drug in solution (usually 0)

K_0 : Zero-order release constant (units: concentration/time)

02. First order model ————— $\log C = \log C_0 - Kt / 2.303$

C_0 : Initial drug concentration

C : Concentration at time t

K : First-order rate constant

03. Higuchi model ————— $Q = Kt^{(1/2)}$

Q : Amount of drug released

K : Higuchi dissolution constant

04. Hixson-Crowell model ————— $W_0^{1/3} - W_t^{1/3} = \kappa t$

W_0 : Initial amount of drug in the dosage form

W_t : Remaining amount at time t

κ : Constant accounting for surface-volume relationship

05. Korsmeyer-Peppas model ————— $M_t / M_\infty = Kt^n$

M_t / M_∞ : Fraction of drug released at time t

K : Release rate constant

n : Release exponent indicating mechanism

Results

Characterization of CaCO_3 Nanoparticles

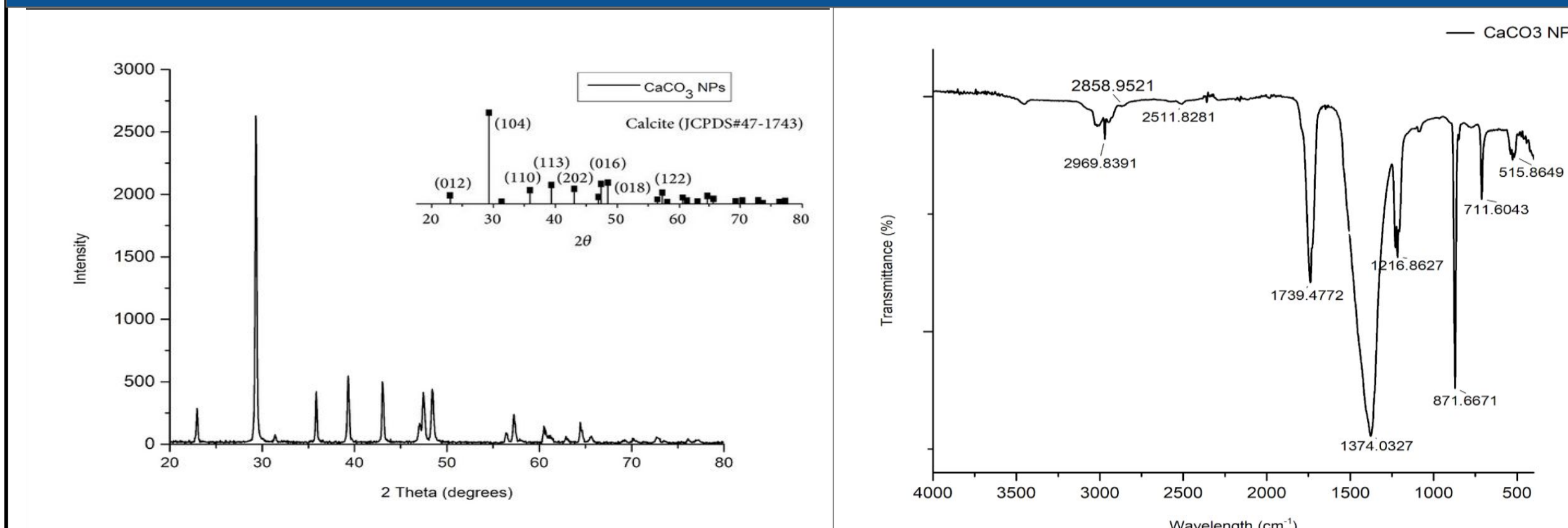


Fig. 01: (a) XRD and (b) FTIR analysis for synthesized nanoparticles

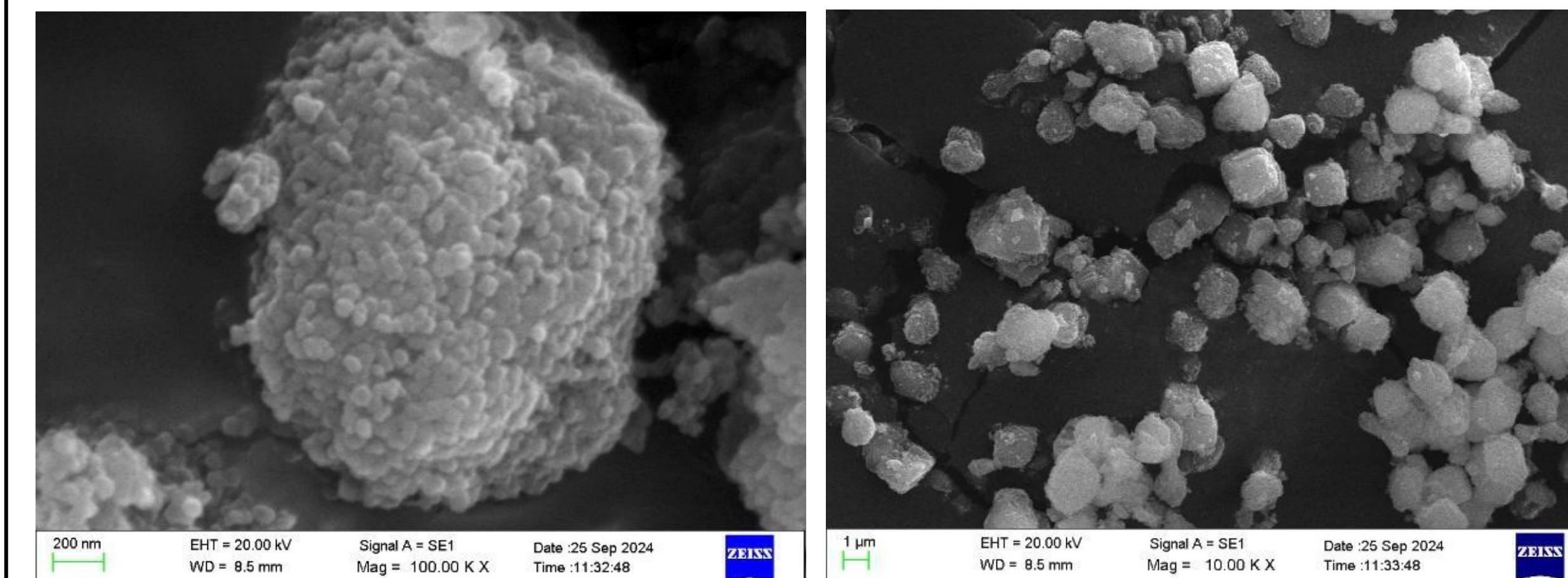


Fig. 02: (a) SEM (*100KX) and (b) SEM (*10KX) analysis for synthesized NPs

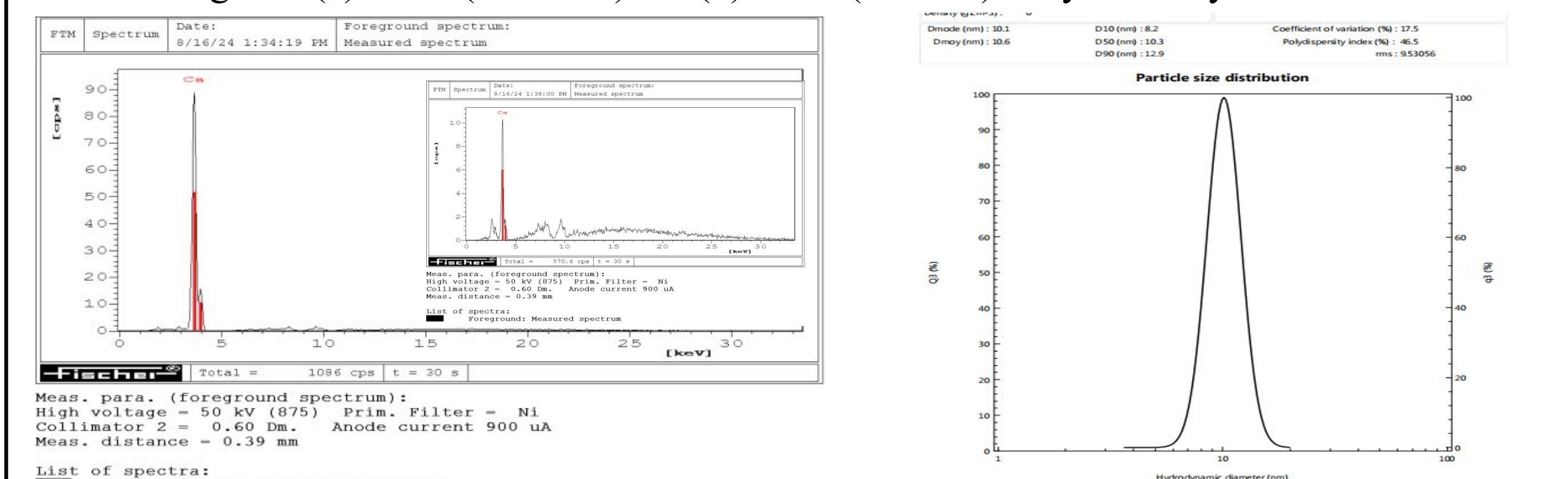


Fig. 03: (a) XRF analysis (b) Particle size analysis for synthesized NPs

Characterization of CHX/ CaCO_3 Nanoparticles

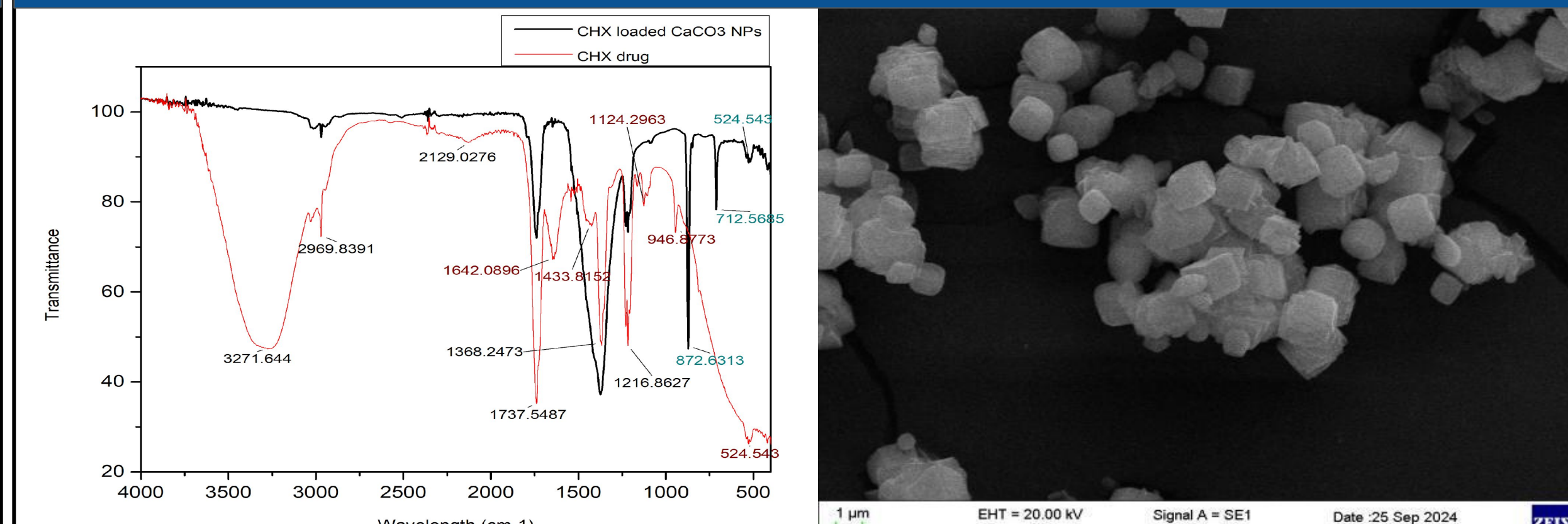


Fig. 04: (a) XRD and (b) SEM analysis for CHX loaded CaCO_3 nanoparticles

In vitro drug release study for CHX/ CaCO_3 NPs

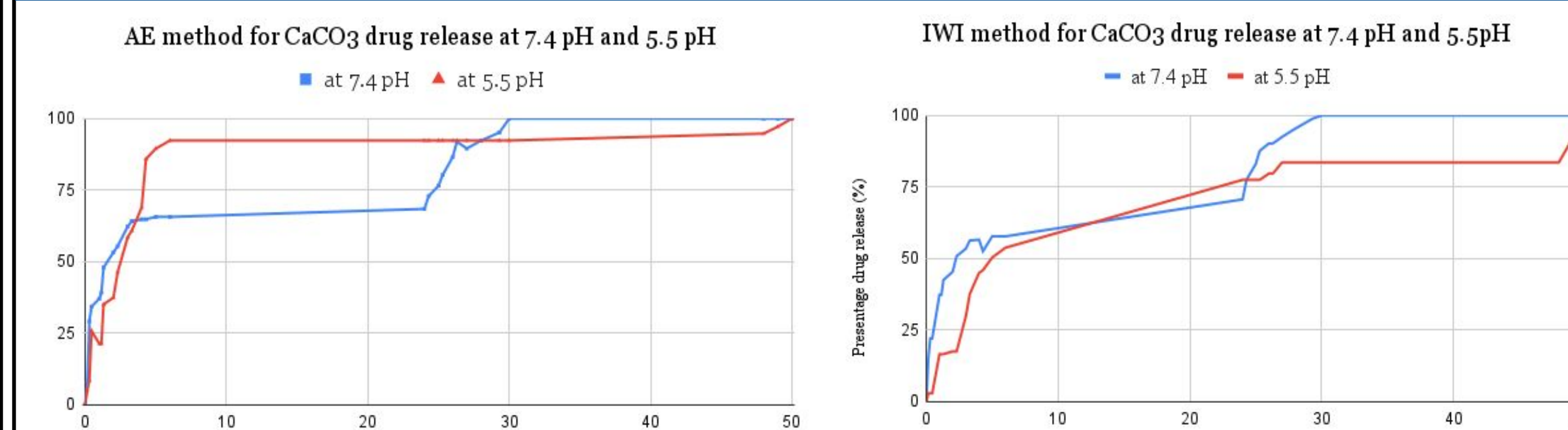


Fig. 05: pH dependent *In vitro* CHX drug release of CHX/ CaCO_3 NPs

Kinetics models for CHX/ CaCO_3 NPs

Table 01: Regression coefficients for mathematical models for prepared formulations

Drug loading method/ pH	Zero-order model	First-order model	Higuchi model	Hixson-Crowell model	Korsmeyer-Peppas model
AE/ 7.4 pH	0.763	0.865	0.926	0.249	0.834
AE/ 5.5 pH	0.977	0.902	0.943	0.963	0.948
IWI/ 7.4 pH	0.766	0.837	0.935	0.221	0.816
IWI/ 5.5 pH	0.962	0.958	0.905	0.685	0.960

Discussion

- XRD analysis indicated an average crystallite size of CaCO_3 as 35.2 nm, while SEM analysis indicated an average particle size of approximately 48.2 nm as determined by ImageJ software. FTIR spectra confirmed the presence of CO_3^{2-} (calcite) and the C-H functional group, and CHX/ CaCO_3NPs showed additional peaks associated with CHX binding. EDXRF analysis confirmed the absence of hazardous materials.
- The IWI method achieved higher drug entrapment efficiency (46.8%) compared to the AE method (18.3%). In vitro drug release studies were conducted by the dialysis method in both acidic (pH 5.5) and neutral (pH 7.4) buffer saline for 50 hours. At 5.5 pH, drug release from both methods followed a zero-order mathematical model, indicating a constant initial drug release within duration. In contrast, the 7.4 pH drug-loaded samples were described by the Higuchi model, suggesting a diffusion-controlled mechanism upto 30 hours.

Conclusion

This study presents a novel and facile approach to forming drug-loaded CaCO_3NPs using natural dolomite. The IWI method obtained high drug-loading capacity, pH-sensitive drug carrier behavior, and controlled drug release at an acidic environment by developing an enhanced oral drug delivery system.

Reference

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