SERS-Assisted Multivariate Data Analysis of SPM-Cu(II) Complex Released in Blood Serum from Stimuli-Responsive Drug Carrier: *In-Vitro* Kinetics Modeling and Pharmacodynamic Analysis

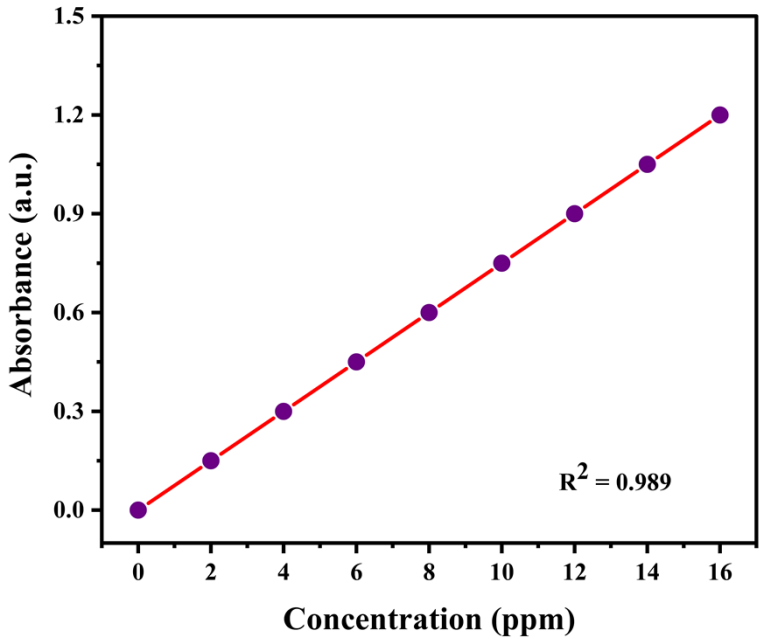

Fig. S1: UV-Vis spectrophotometer calibration curve for SPM-Cu(II) Complex.

Table 1: Comparative analysis between cited reported work (Plasmonics 2025) [1] and Present Study.

Parameters	**Plasmonics (2025)** [1]	**Present Study**	**Scientific Advancement**
Core Objective	Structural & comparative evaluation of SPM and metal complexes	Quantitative therapeutic release modeling in biological matrix	Shift from molecular characterization to translational monitoring

Release Medium	PBS (simple buffer system)	Human blood serum (complex biological matrix)	Clinically relevant matrix
SERS Role	Spectral differentiation & discrimination	Validated quantitative analytical platform	Functional analytical advancement
Chemometrics	PCA, PLS-DA, limited PLSR to complexes only	PCA, HCA, full PLSR with regression equation, RMSEC, RMSEP to complex in serum	Advanced predictive modeling
LOD / LOQ	Not calculated	Explicitly calculated	Analytical validation
Cross-validation	Basic	Leave-one-out (LOOCV)	Statistical robustness
Kinetics Modeling	Model fitting only	ANOVA-supported discrimination between models	Mechanistic confirmation
Diffusion Mechanism	General release behavior	Confirmed Fickian diffusion in serum (n = 0.463)	Mechanistic validation in biological matrix
Biological Evaluation	Activity of synthesized complexes	Activity of serum-released complex	Therapeutic relevance
Pharmacodynamic Correlation	Independent biological tests	Direct correlation of release concentration with MIC/MBC/biofilm	Integrated PK-PD perspective

Cytotoxicity Context	Complex-based	Serum-released complex-based	Realistic exposure model
Translational Level	Material characterization	Drug delivery and therapeutic modeling platform	Conceptual progression

However, unlike in our previous study, where comparative SERS monitoring was performed, DFT analysis and biological evaluation of spectinomycin-metal complexes in simplified systems, the current study is able to go ahead and present a clinically relevant release model of a stimuli-sensitive hydrogel matrix into serum. It is a combination of actual biological matrix measurements, multivariate predictive modeling, diffusion-regulated kinetic validation, and pharmacodynamic correlation, thus transforming the spectroscopic monitoring into a therapeutic delivery platform.

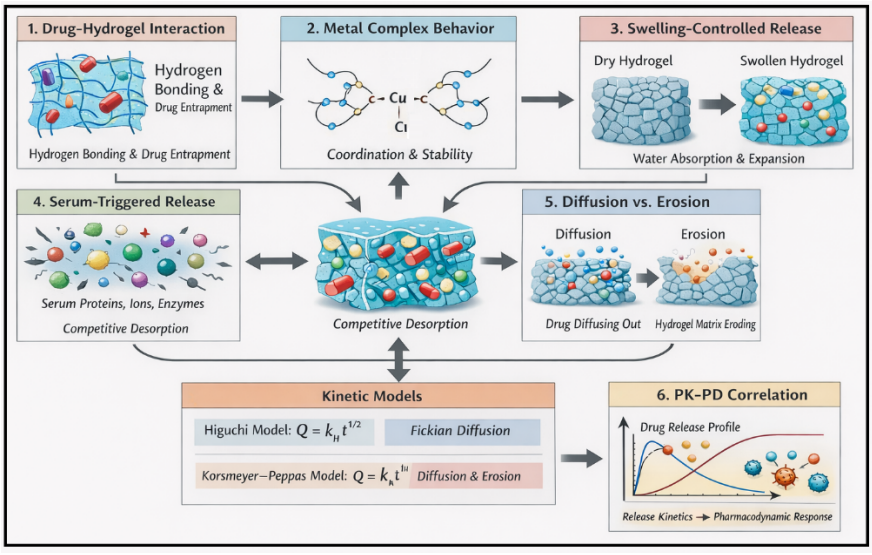

Fig. S2: Mechanistic illustration of controlled SPM-Cu(II) release by PVA/AgO hydrogel in human serum. The kinetics of release resemble Higuchi and Korsmeyer-Peppas diffusion-dominated (Fickian) models, which confirm that the release is diffusion-associated and allows the correlation of release profile with pharmacodynamics.

Table S2: Comparative analysis of recent controlled drug release systems and analytical monitoring approaches.

Drug	**Carrier Material**	**Analytical Monitoring**	**Release Behavior**	**Biological Validation**	**Key Advantage**	**Ref**
Spectinomycin -Cu(II) Complex	PVA/AgO hydrogel	SERS + PLSR	Sustained (serum/PBS)	ZOI, MIC, MBC, Cytotoxicity, Hemolytic	Real-time quantitative SERS validation	This work
Doxorubicin	chitosan/g-C_3N_5/ferrite	UV-Vis	Controlled	Antibacterial	pH-responsive release	[2]
Gentamicin	g-C_3N_5/Starch/carboxymethyl cellulose composite	UV-Vis	Sustained	*In-vitro* assays	Enhanced bioavailability	[3]
Amoxicillin	hydroxyapatite -calcium ferrite composite	Spectroscopy	Controlled	Biocompatibility tested	High stability	[4]
Metronidazole	calcium ferrite-carbon nanotubes carrier	Surface analysis	Sustained antimicrobial	Antimicrobial	Enhanced durability	[5]

References

1. A. Naman, N. Mehmood, A. Fatima, M. Kim, S. Knani, M. E. Safadi and S. Younas, Plasmonics, 2025, 1-27.
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