Evaluation of the effectiveness of inclusion complexes with cyclodextrins for improving the solubility and bioavailability of drugs: A meta-analysis

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Supplementary Material

Table S1: Studies excluded following full text screening

Author, year	Title	Reason	Detail
Su et al., 2020	Inhalation of Tetrandrine-hydroxypropyl-β-cyclodextrin Inclusion Complexes for Pulmonary Fibrosis Treatment	Route of administration	Intratracheal administration
Z. Wang & Li, 2018a	Raloxifene/SBE-β-CD Inclusion Complexes Formulated into Nanoparticles with Chitosan to Overcome the Absorption Barrier for Bioavailability Enhancement	Route of administration	Intragastrical administration
Ren et al., 2019	Preparation, optimization of the inclusion complex of glaucocalyxin A with sulfobutylether-β-cyclodextrin and antitumor study	Route of administration	Intravenous administration
M. Chen et al., 2017	Preparation, characterization and in vivo evaluation of a formulation of dantrolene sodium with hydroxypropyl—cyclodextrin	Route of administration	Intragastric administration
X. Chen et al., 2010	Enhanced aqueous solubility and bioavailability of capsaicin by the preparation of an inclusion complex	Route of administration	Subcutaneous administration
Ren et al., 2020	Inclusion Complex of Docetaxel with Sulfobutyl Ether β-Cyclodextrin: Preparation, In Vitro Cytotoxicity and In Vivo Safety	Route of administration	Tail injection

N. Li et al., 2018	Preparation of curcumin-hydroxypropyl-β-cyclodextrin inclusion complex by cosolvency-lyophilization procedure to enhance oral bioavailability of the drug	Route of administration	Intravenous administration
Manne et al., 2021	Hot liquid extrusion assisted drug-cyclodextrin complexation: a novel continuous manufacturing method for solubility and bioavailability enhancement of drugs	Species	Wistar rats were used for this study
D. Xu et al., 2021	Preparation, characterization and pharmacokinetic studies of sulfobutyl ether-β-cyclodextrin-toltrazuril inclusion complex	Species	Broilers were used for this study
L. Zhang et al., 2020	In Vitro and In Vivo Comparison of Curcumin-Encapsulated Chitosan-Coated Poly (lactic-co-glycolic acid) Nanoparticles and Curcumin/Hydroxypropyl-β-Cyclodextrin Inclusion Complexes Administered Intranasally as Therapeutic Strategies for Alzheimer's Disease	Species	C57BL/6 mice were used for this study
Erdoğar et al., 2020	Improved oral bioavailability of anticancer drug tamoxifen through complexation with water soluble cyclodextrins: in vitro and in vivo evaluation	Species	Balb-c mice were used for this study
Lodagekar et al., 2019	Formulation and evaluation of cyclodextrin complexes for improved anticancer activity of repurposed drug: Niclosamide	Species	Balb-c mice were used for this study

W. Zhang et al., 2019	MOF Capacitates Cyclodextrin to Mega-Load Mode for High-Efficient Delivery of Valsartan	Species	Beagle dogs were used for this study
Creteanu et al., 2019	Study on the Role of the Inclusion Complexes with 2-Hydroxypropyl-*β*-cyclodextrin for Oral Administration of Amiodarone	Species	Wistar rats were used for this study
Al-Gethmy et al., 2019	Optimization of the Factors Affecting the Absorption of Vardenafil from Oral Disintegrating Tablets: A Clinical Pharmacokinetic Investigation	Species	Human were used for this study
Fan et al., 2019	Comparative muscle irritation and pharmacokinetics of florfenicol-hydroxypropyl-β-cyclodextrin inclusion complex freeze-dried powder injection and florfenicol commercial injection in beagle dogs	Species	Beagle dogs were used for this study
Purpura et al., 2018	Analysis of different innovative formulations of curcumin for improved relative oral bioavailability in human subjects	Species	Human were used for this study
L. Zhang et al., 2018	The hydroxypropyl–β-cyclodextrin complexation of toltrazuril for enhancing bioavailability	Species	Rabbits were used for this study
D. Wang et al., 2017	Preparation and Characterization of the Sulfobutylether-β-Cyclodextrin Inclusion Complex of Amiodarone Hydrochloride with Enhanced Oral Bioavailability in Fasted State	Species	Beagle Dogs were used for this study

Mady & Farghaly Aly, 2017	Experimental, molecular docking investigations and bioavailability study on the inclusion complexes of finasteride and cyclodextrins	Species	Albino rabbits were used for this study
Darekar et al., 2016	Characterization and in vivo evaluation of lacidipine inclusion complexes with β-cyclodextrin and its derivatives	Species	Wistar rats were used for this study
Dahiya et al., 2015	Improved Pharmacokinetics of Aceclofenac Immediate Release Tablets Incorporating its Inclusion Complex with Hydroxypropyl-β-Cyclodextrin	Species	Wistar rats were used for this study
Gidwani & Vyas, 2015	Inclusion complexes of bendamustine with β -CD, HP- β -CD and Epi- β -CD: in-vitro and in-vivo evaluation	Species	Wistar rats were used for this study
Ren et al., 2014	Preparation and Pharmacokinetic Study of Aprepitant–Sulfobutyl Ether-β-Cyclodextrin Complex	Species	Beagle dogs were used for this study
J. Wu et al., 2013	Sulfobutylether-β-cyclodextrin/chitosan nanoparticles enhance the oral permeability and bioavailability of docetaxel	Species	Wistar rats were used for this study
Ridhurkar et al., 2013	Inclusion complex of aprepitant with cyclodextrin: Evaluation of physico-chemical and pharmacokinetic properties	Species	Human were used for this study
C. Wu et al., 2013	Comparative pharmacokinetics and bioavailability of four alkaloids in different formulations from Corydalis Decumbens	Species	Wistar rats were used for this study

Chauhan et al., 2013	Inclusion complex of colchicine in hydroxypropyl-β-cyclodextrin tenders better solubility and improved pharmacokinetics	Species	Mice were used for this study
Zeng et al., 2013	In vitro and in vivo characterization of amorphous, nanocrystalline, and crystalline ziprasidone formulations	Species	Beagle dogs were used for this study
Hwang et al., 2012	Characterization, stability, and pharmacokinetics of sibutramine/b-cyclodextrin inclusion complex	Species	Human were used for this study
Huang et al., 2011	Pharmacokinetics, Efficacy, and Safety Evaluation of Docetaxel/Hydroxypropyl-Sulfobutyl-β-Cyclodextrin Inclusion Complex	Species	Albino rabbits were used for this study
Ansari et al., 2011	Improving the solubility and bioavailability of dihydroartemisinin by solid dispersions and inclusion complexes	Species	Swiss mice were used for this study
Ribeiro et al., 2010	Prolonged Absorption of Antimony(V) by the Oral Route from Non-inclusion Meglumine Antimoniate– β -cyclodextrin Conjugates	Species	Beagle dogs were used for this study
Žmitek et al., 2008	Relative bioavailability of two forms of a novel water-soluble coenzyme Q10	Species	Human were used for this study
Yan et al., 2008	Characterization and In Vivo Evaluation of an Inclusion Complex of Oridonin and 2-hydroxypropyl- β -cyclodextrin	Species	Wistar rats were used for this study

Tayade & Vavia, 2006	Inclusion complexes of Ketoprofen with beta-cyclodextrins: Oral pharmacokinetics of Ketoprofen in human	Species	Human were used for this study
Ghorab et al., 2004	Tablet formulation containing meloxicam and β-cyclodextrin: Mechanical characterization and bioavailability evaluation	Species	Human were used for this study
Géczy et al., 2000	The inclusion of fluoxetine into γ-cyclodextrin increases its bioavailability: behavioural, electrophysiological and pharmacokinetic studies	Species	Human were used for this study
J. Li et al., 2021	Rational formulation engineering of fraxinellone utilizing 6-O-α-D-maltosyl-β-cyclodextrin for enhanced oral bioavailability and hepatic fibrosis therapy	Species	Wistar rats were used for this study
Y. Xu et al., 2019	Chloramphenicol/sulfobutyl ether-β-cyclodextrin complexes in an ophthalmic delivery system: prolonged residence time and enhanced bioavailability in the conjunctival sac	Species	Rabbits were used for this study
Ding et al., 2019	Pharmacokinetics and liver uptake of three Schisandra lignans in rats after oral administration of liposome encapsulating β-cyclodextrin inclusion compound of Schisandra extract	Species	Wistar rats were used for this study
H.-B. Wang et al., 2017	A pH-independent instantaneous release of flurbiprofen: a study of the preparation of complexes, their characterization and in vitro/in vivo evaluation	Species	Wistar rats were used for this study

Leonardi et al., 2013	Effects of benznidazole:cyclodextrin complexes on the drug bioavailability upon oral administration to rats	Species	Wistar rats were used for this study
Zeng et al., 2013	Formulation and in vivo evaluation of orally disintegrating tablets of clozapine/hydroxypropyl-β-cyclodextrin inclusion complexes	Species	Rabbits were used for this study
Frézard et al., 2008	Enhanced oral delivery of antimony from meglumine antimoniate/β-cyclodextrin nanoassemblies	Species	Beagle dogs were used for this study
Patel & Rajput, 2009	Enhancement of Oral Bioavailability of Cilostazol by Forming its Inclusion Complexes	Species	New Zealand rabbits were used for this study
Nie et al., 2007	In Vitro and in vivo studies on the complexes of vinpocetine with hydroxypropyl-β-cyclodextrin	Species	Rabbits were used for this study
Hassan et al., 2007	Enhancement of dissolution amount and *in vivo* bioavailability of itraconazole by complexation with β-cyclodextrin using supercritical carbon dioxide	Species	Wistar rats were used for this study
Piette et al., 2006	Pharmacokinetic study of a new synthetic MMP inhibitor (Ro 28-2653) after IV and oral administration of cyclodextrin solutions	Species	Sheep were used for this study
Evrard et al., 2002	Oral bioavailability in sheep of albendazole from a suspension and from a solution containing hydroxypropyl-β-cyclodextrin	Species	Sheep were used for this study

Miyake et al., 2000	Improvement of Solubility and Oral Bioavailability of Rutin by Complexation with 2-Hydroxypropyl-b-cyclodextrin	Species	Beagle dogs were used for this study
Veiga et al., 2000	Oral bioavailability and hypoglycaemic activity of tolbutamide/cyclodextrin inclusion complexes	Species	Rabbits were used for this study

Table S2: Molecular docking results of the studies included

Study	Treatment formulations	Binding Energy (Kcal/mol)
Tian et al., 2020	Isorhamnetin/HP-β-CD	-6.15
	Kaempferol/HP-β-CD	-6.37
	Quercetin/HP-β-CD	-6.65
R. Li et al., 2019	[6]-Shogaol/β-CD	-4.82
Xu et al., 2014	Honokio/SB-β-CD	-7.15
Liu et al., 2013	β-Caryophyllene/β-CD	-6.00
Kong et al., 2018	Simvastatin/HP-β-CD	-7.62
	Atorvastatin calcium/HP-β-CD	-2.70
Lee et al., 2006	Ginseng saponin/β-CD	-4.42
Xie et al., 2013	Puerarin/HP-β-CD	-6.08
Zuo et al., 2002	Flutamide/HP-β-CD	-4.28
Hu et al., 2021	Koumine/HP-β-CD	-7.35
Wang & Li, 2018	Raloxifene/SBE-β-CD	-7.85
Igami et al., 2016	Compound K/γ-CD	-6.44
	Compound K/β-CD	-7.22

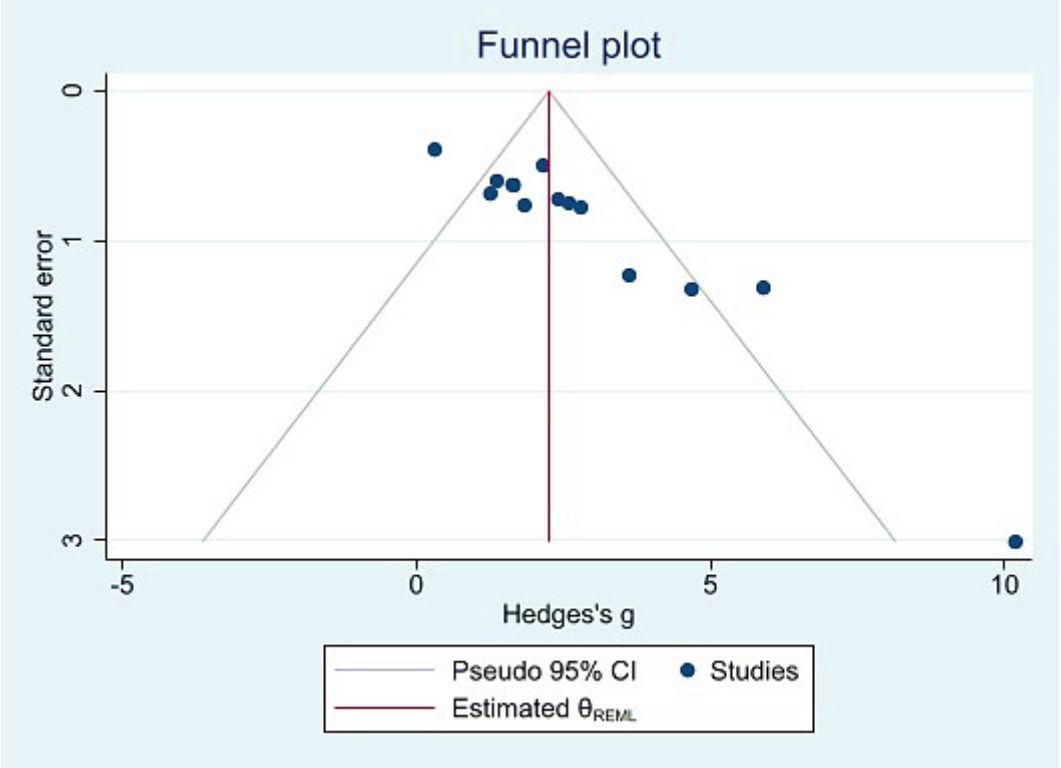


Figure S1: Funnel plot showing estimates of maximum concentration of a drug (C_{max}) in the meta-analysis of the evaluation of the effectiveness of inclusion complexes with cyclodextrins for improving the solubility and bioavailability of drugs based on studies published before 2024.

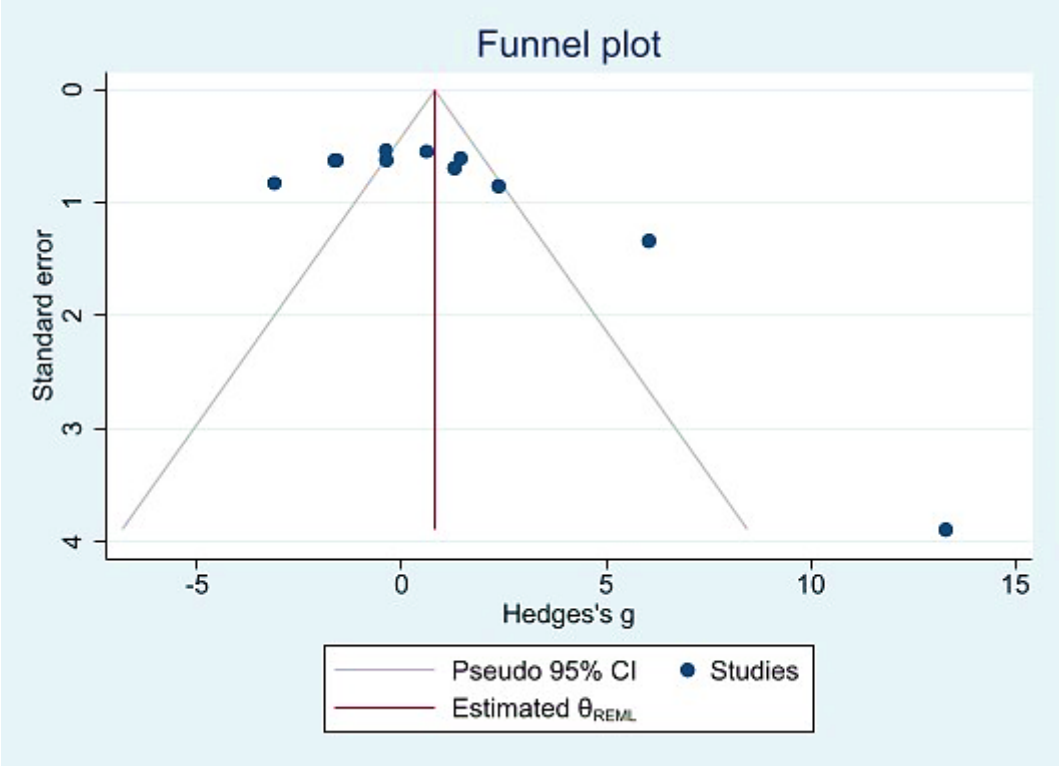


Figure S2: Funnel plot showing estimates of the half-life ($T_{1/2}$) in the meta-analysis of the evaluation of the effectiveness of inclusion complexes with cyclodextrins for improving the solubility and bioavailability of drugs based on studies published before 2024.

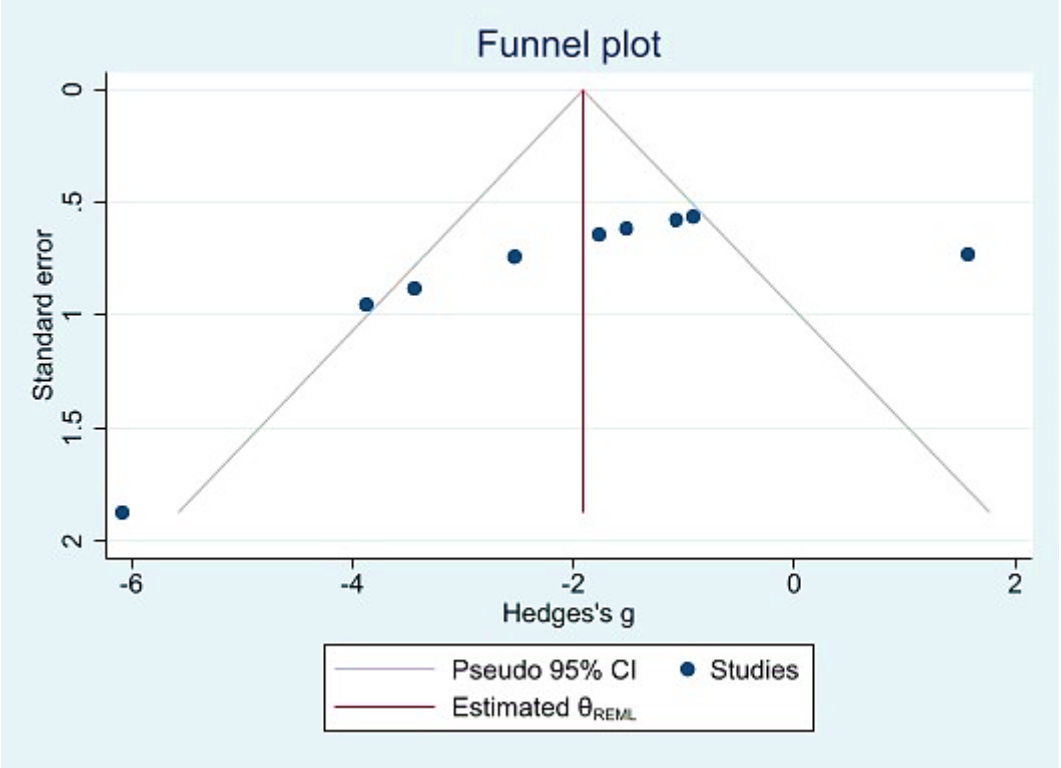


Figure S3: Funnel plot showing estimates of the peak time (T_{max}) in the meta-analysis of the evaluation of the effectiveness of inclusion complexes with cyclodextrins for improving the solubility and bioavailability of drugs based on studies published before 2024.

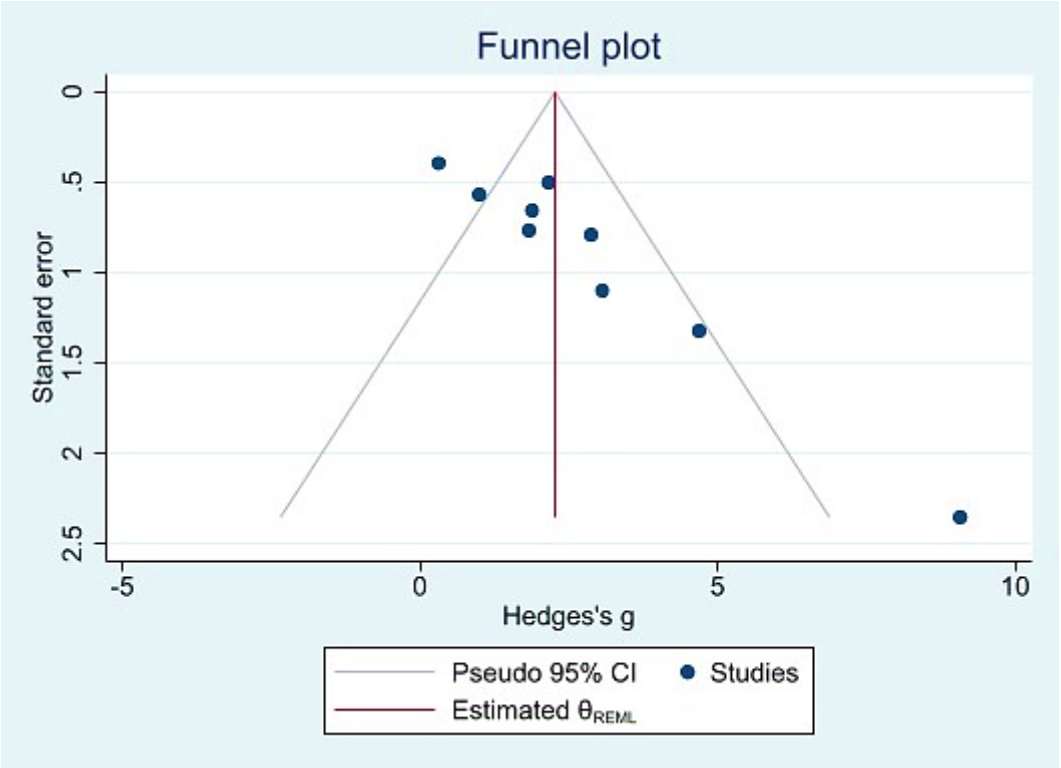


Figure S4: Funnel plot showing estimates of the area under the curve (AUC) in the meta-analysis of the evaluation of the effectiveness of inclusion complexes with cyclodextrins for improving the solubility and bioavailability of drugs based on studies published before 2024.

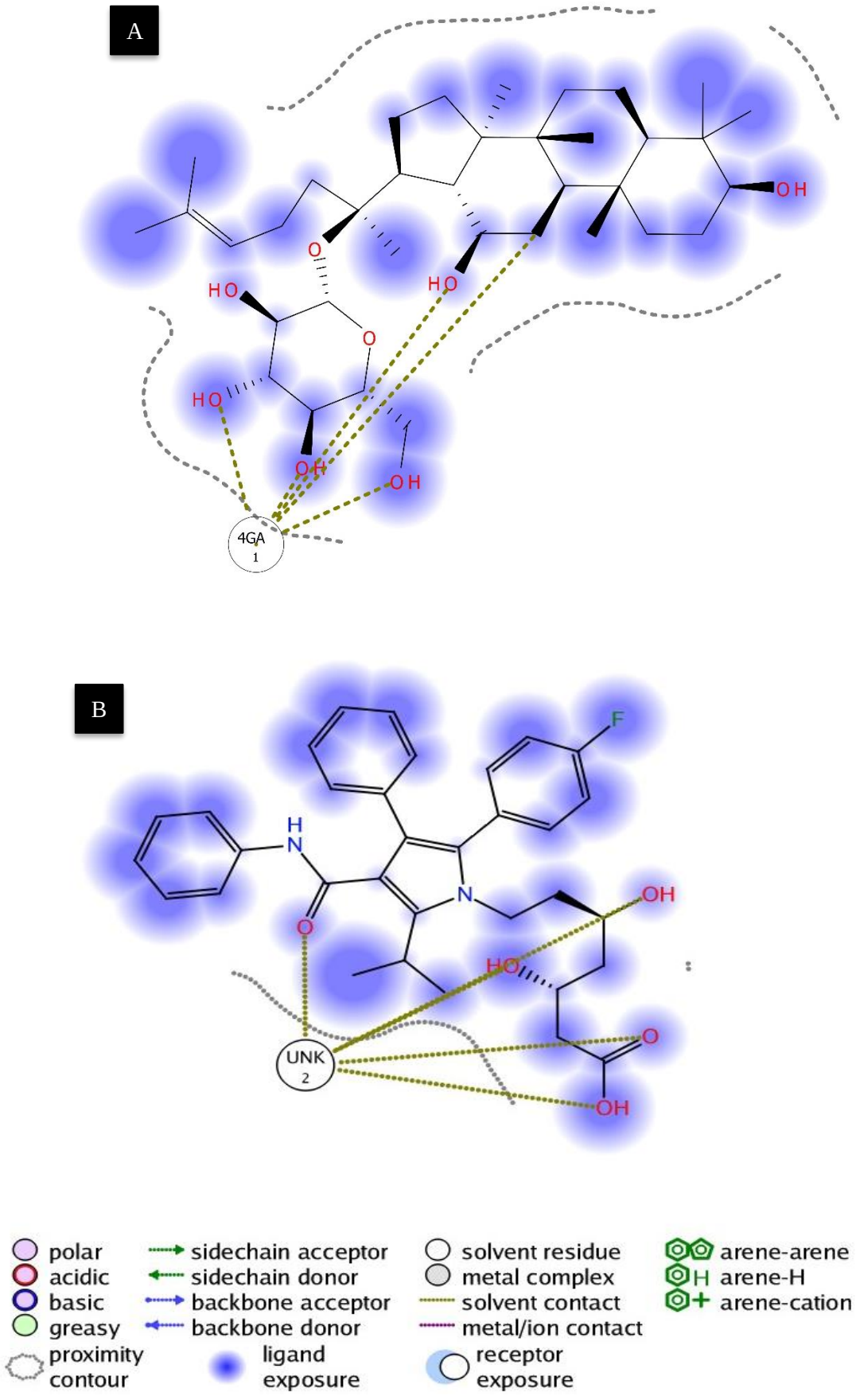


Figure S5: Receptor–ligand interaction (2D) diagrams of compound K (A), and atorvastatin (B) with HP-β-CD and β-CD, respectively.

Chemoinformatics modeling

The molecular analysis and visualization operations were performed employing the Python RDKit toolkit. SMILES strings were used to represent the chemical structures of the ligands (n = 2), and the RDKit Chem module allowed the analysis. The topological polar surface area (TPSA) values, which is obtained from the sum of fragment contributions (partial charges of oxygen and nitrogen). TPSA was reported to be a reliable descriptor that characterizes drug absorption, bioavailability, and permeability (Khalid et al., 2024). The following is the equation used to determine the TPSA:

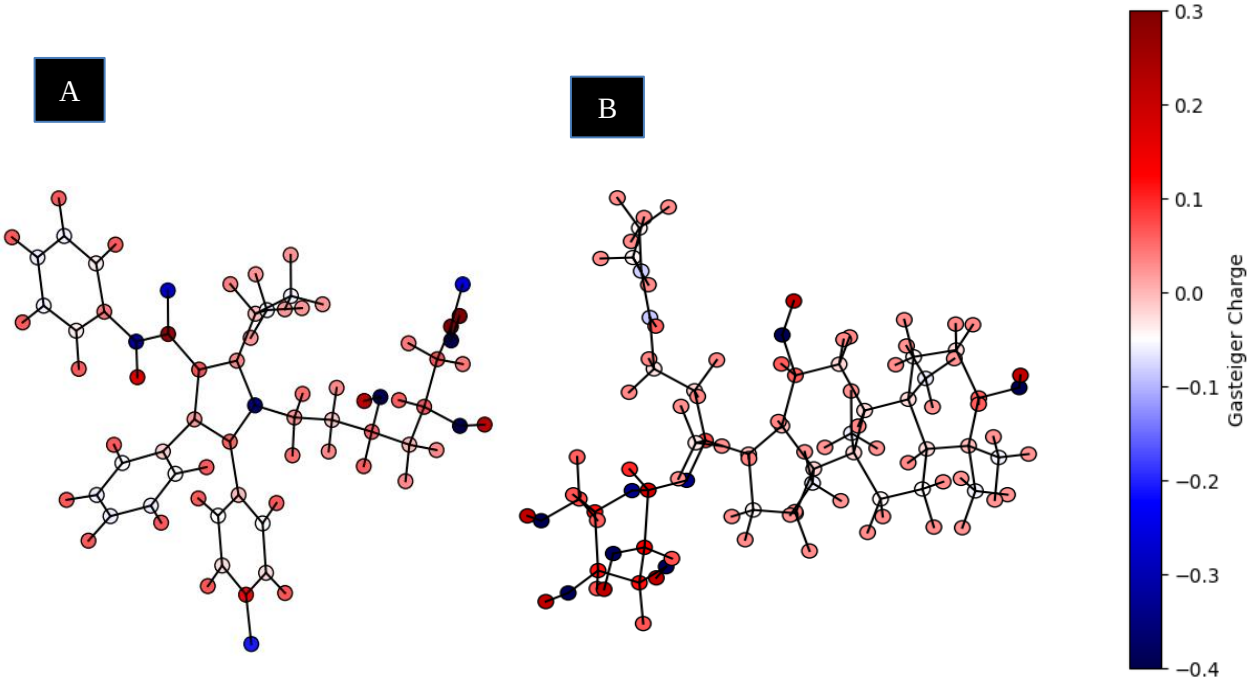
$$TPSA = \sum_i (\frac{1}{2} \times area_i)$$

with TPSA denoting the topological polar surface area and $area_i$ denoting the contribution of the i^{th} polar atom to the total surface area.

The electronegativity of atoms and their immediate surroundings inside molecules serve as the foundation for the Gasteiger partial charge computation technique. The equation to calculate the Gasteiger charges is given by:

$$q_i^t = q_i^0 + \sum_{j \neq i} \frac{d_{ij} \times q_j^{t-1} \times f_{ij}}{\sqrt{d_{ij}^2}}$$

With q_i^t denoting the Gasteiger charge on atom *i* at iteration *t*; q_i^0 denoting the initial charge on atom *i*; q_j^{t-1} denoting the Gasteiger charge on neighboring atom *j* at the previous iteration *t-1*; d_{ij} denoting the Euclidean distance between atoms *i* and *j*; and f_{ij} is the resonance correction factor between atoms *i* and *j*.



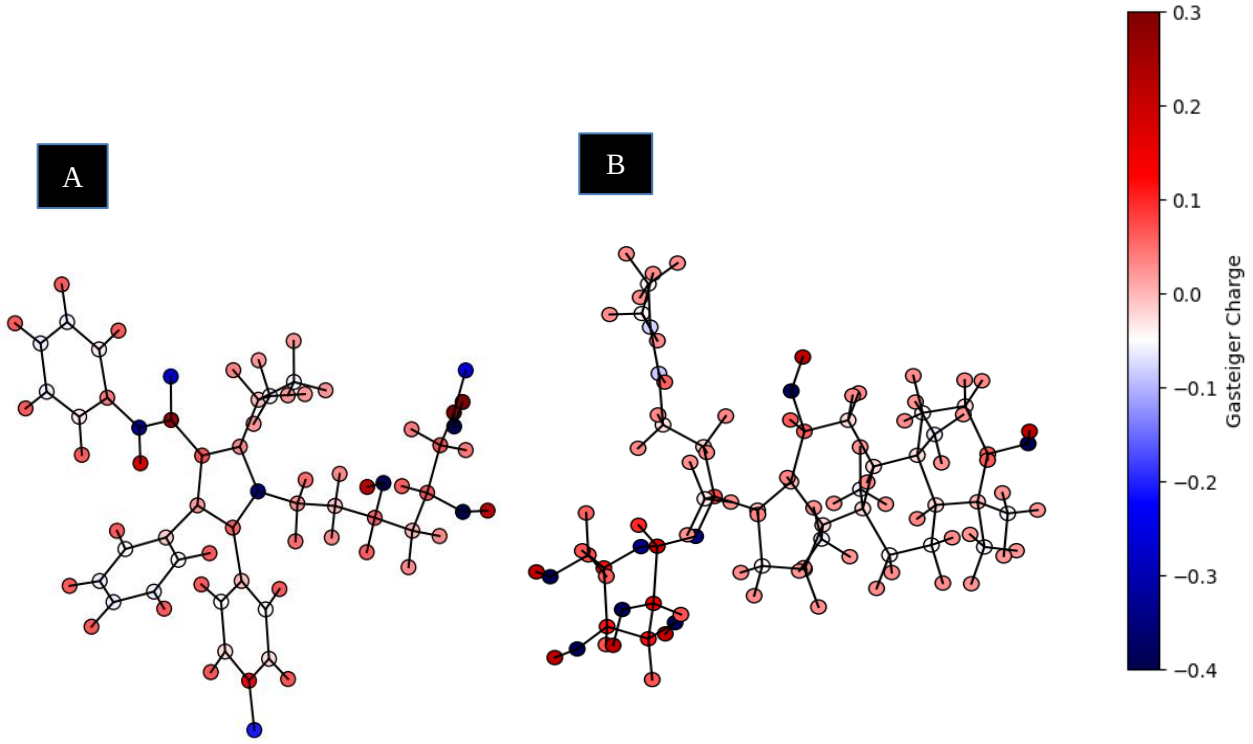
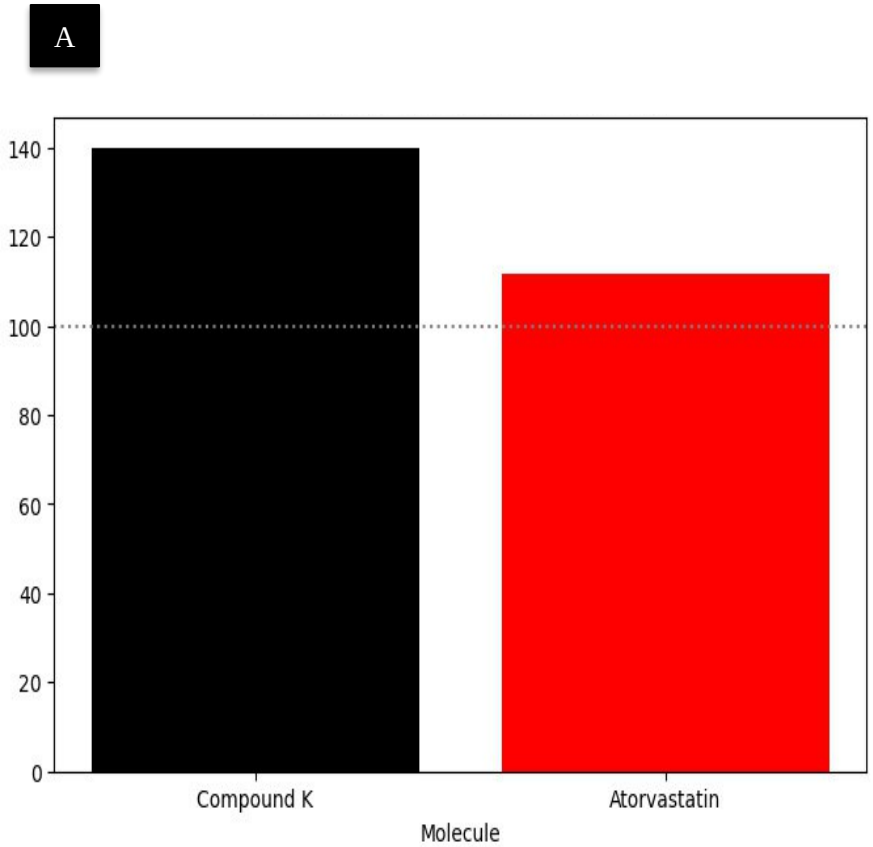


Figure S6: TPSA and Gasteiger charge representations for (A) atorvastatin calcium and (B) compound K.



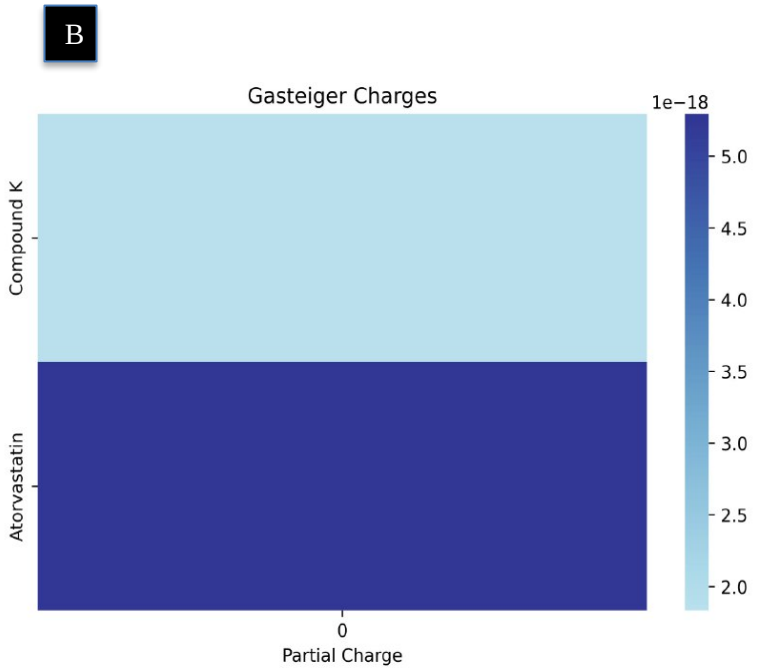


Figure S7: TPSA (A) and Gasteiger charge (B) values for the analyzed ligands. The TPSA threshold is depicted as a dashed line.

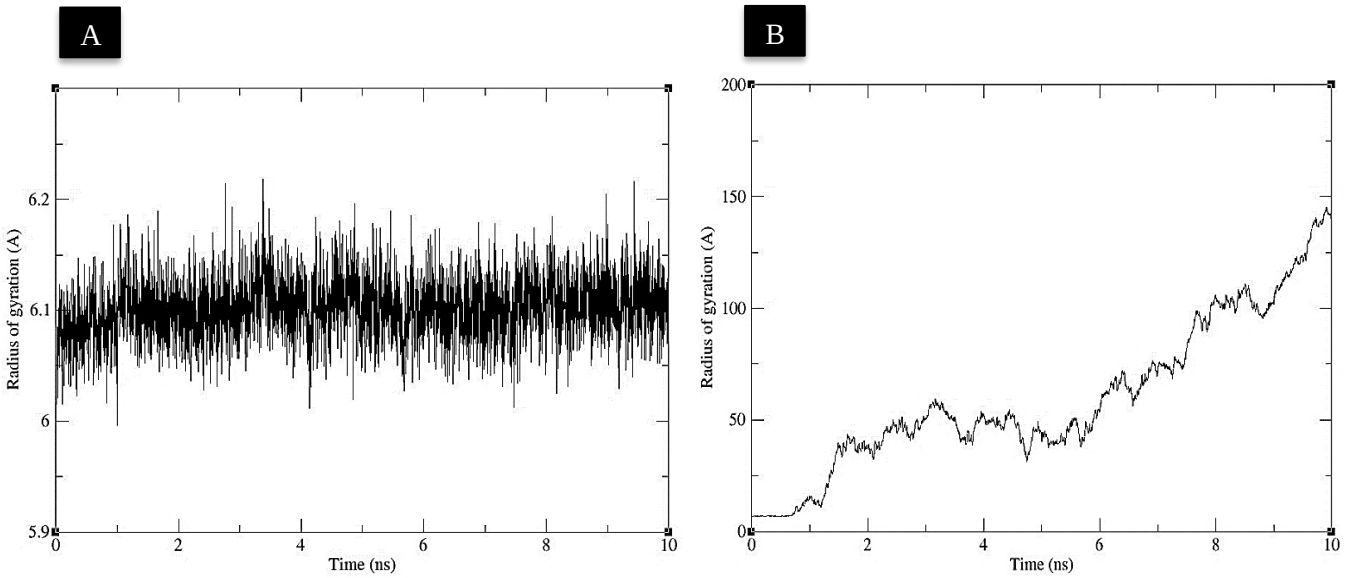


Figure S8: Rg for the compound K/ β-CD (A) and atorvastatin calcium/HP-β-CD (B) complexes during 10 ns of MD simulation.

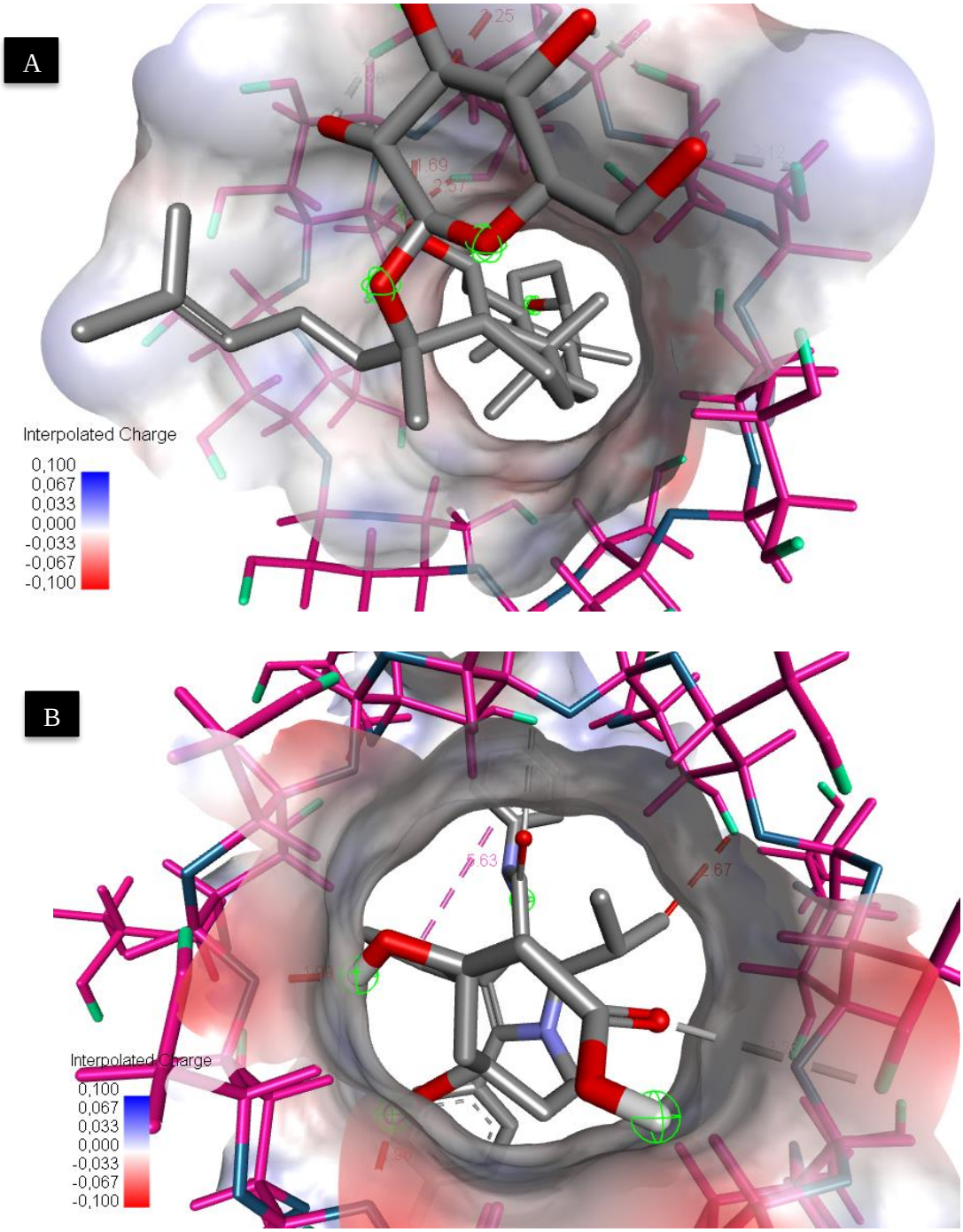


Figure S9: Predicted interpolated surface charges of compound K/ β-CD (A) and atorvastatin calcium/HP-β-CD (B) complexes

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