Original Article

Molecular docking studies of curcumin with β-cyclodextrins to investigate pre-formulation perspective to overcome bioavailability problems

Rajib Das, Kankan Roy, Ankit Kumar Rai, Sant Kumar Verma*

Department of Pharmaceutical Chemistry, ISF College of Pharmacy, Moga, Punjab, India

Correspondence:
Sant Kumar Verma, Department of Pharmaceutical Chemistry, ISF College of Pharmacy, Moga, Punjab, India. E-mail: santkumarverma@isfcp.org

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ABSTRACT

β-cyclodextrin (β-CD) are used to form host-guest inclusion complexes with poorly water-soluble drugs in solution or a solid-state. Inclusion complexes formed with a host-guest molecule may exhibit improved chemical or biological properties compared to the host molecule alone. Such inclusion may improve aqueous solubility, dissolution, and bioavailability. However, the use of CDs is limited in some cases because it is very difficult, to identify the most suitable CD as a host complexing agent for a particular drug, to map whether the guest molecule is fitted partially or completely within the core of CD, and to predict the classic stereo-structure of the polymer and the forces between host and guest complex. Owing to low aqueous solubility of β-CD (18 g/L), its higher water-soluble analogs such as hydroxypropyl, sulfobutyl ether (SE), and methyl β-CDs are most favored for complexation. In the present study, highest water-soluble β-CD, i.e., (SE β-CD, solubility ~700g/L g/L) was selected for *in silico* complexation studies with curcumin, compared to conventional β-CD, using molecular docking studies. The results of *in silico* affinity and interaction studies showed that SE β-CD has more affinity for curcumin compared to β-CD in terms of MolDock score. This computational study may be used as a guide for pre-formulation prospective of curcumin to overcome the solubility and bioavailability problems associated.

Keywords: Curcumin, *in silico* complexation, molecular docking, sulfobutyl ether β-cyclodextrin

INTRODUCTION

Curcumin, also called diferuloylmethane, is chemically a bis-α,β-unsaturated β-diketone named 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione [Figure 1]. It is the main natural hydrophobic polyphenol found in the rhizome of the herb *Curcuma longa* (turmeric).[1] Curcumin exhibits keto–enol tautomerism [Figure 2] having a predominant keto form in acidic and neutral solutions and stable enol form in alkaline medium.[2] Curcumin has been reported for wide spectrum of biological and pharmacological activities including anti-inflammatory, antioxidant, antimicrobial, anti-diabetic, anticancer, antirheumatic, anti-thrombotic, hepato-, nephro-, and cardio protective.[3-23] Various animal models[24,25] or human studies.[26-29] proved that curcumin is extremely safe even at very high doses. The pharmacological safety and efficacy of curcumin make it a potential compound for the treatment and prevention of a wide variety of human diseases. In spite of its efficacy and safety, curcumin has not yet been approved as a therapeutic agent, and the poor bioavailability of curcumin has been highlighted as a major problem for this. Lower absorption, rapid metabolism, and in turn rapid elimination are the major factors for the poor bioavailability of curcumin.

The common approaches to enhance the bioavailability of poorly water-soluble drugs are micronization, the use of surfactant, and the solid dispersion prepared with cyclodextrins (CDs).

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CDs are widely used in pharmaceuticals, drug delivery systems, cosmetics, and the food and chemical industries. Their successful use in inclusion complexes with bioactive compounds has led to extensive investigations in several different application areas to try to overcome the limitations of certain substances and drug molecules. The natural CDs α-, β-, and γ-CDs are composed of 6, 7, or 8 glucose units, and their synthetic derivatives are divided into three groups: hydrophilic, such as 2-hydroxypropyl β-CD (HP-β-CD); hydrophobic, such as 2,6-di-O-ethyl-β-CD; and ionizable, such as sulfobutylether β-CD (SBE-β-CD). CDs have the capability to align hydrophobic molecules as a host-guest complex due to their characteristic structural arrangement. The designing of the inclusion composites drastically alters the physical and chemical properties of the guest moiety, generally in terms of aqueous solubility, and could enhance the bioavailability. However, owing to its low aqueous solubility of β-CD (18 g/L), its higher water-soluble analogs such as HP, sulfobutyl, and methyl β-CDs are most favoured for complexation.[30] Exploration of polymer-drug interactions using molecular docking simulations is an efficient technique to investigate pre-formulation perspective to develop a viable formulation to overcome bioavailability problems of a substance or drug molecule. In this research, *in silico* drug-polymer complexation studies were performed on curcumin and higher water-soluble analog (~700g/L) of β-CD, *i.e.,* sulfobutyl ether (SE) β-CD using molecular docking simulations.

COMPUTATIONAL METHODOLOGY

Molecular modelling and energy optimization

The chemical structure of curcumin was sketched using ChemDraw Ultra 8.0. After structure check and clean up, these 2D conformers were converted into 3D and further subjected to energy minimization by molecular mechanics (MM2) and re-optimized by Hamiltonian approximations Austin model optimizer available in molecular orbital package (MOPAC) module of Chem3D Ultra 8.0. For both the MM2 and MOPAC minimizers, the minimum root-mean-square (RMS) gradient values were set as 0.0001 kcal/mol Å. All the energy-optimized structures were kept in MDL Mol File format for input as ligand molecules *in silico* drug-polymer complexation studies.

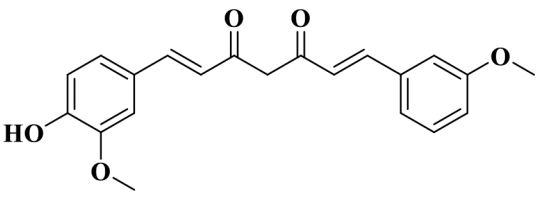

Figure 1: Chemical structure of curcumin

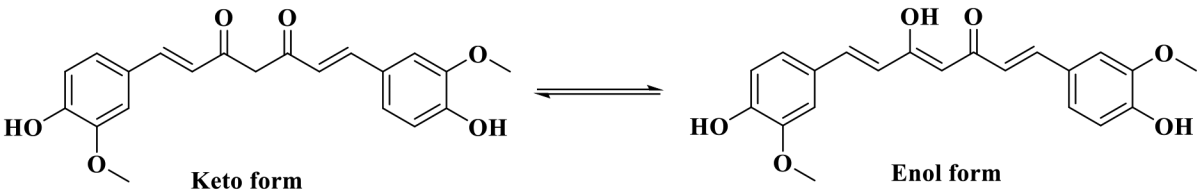

Figure 2: Tautomers of curcumin

Preparation of β-CDs

The higher water-soluble analog of β-CD SE β-CD (PubChem CID 66577045) [Figure 3] was retrieved from PubChem in SDF file format. The β-CDs were transformed in 3D PDB files using VEGA ZZ software.

Search space setup

In silico drug-polymer complexation studies of curcumin and SE β-CD were performed using Molegro Virtual Docker (MVD). The 3D structure of SE β-CD in PDB file format was retrieved into MVD workspace and prepared for geometry optimization including correction in inappropriate bond angle or bond length and any missing bond. The center coordinates of search space were set as X = 78.5 Å, Y = 0.75 Å, Z = –1.50Å with radius 11.0Å.

In silico drug-polymer complexation study

The energy-optimized structure of curcumin was imported in the workspace of MVD for the *in silico* complexation of curcumin and polymer using docking simulation runs. The parameters like grid resolution and binding site radius were set to the values 0.30 Å and 10–15 Å, respectively. A maximum of 1500 iterations, the maximum population size of 50, number of runs 10, algorithm MolDock SE and cluster similar poses RMSD threshold 1.00 Å were fixed, whereas other parameters were kept as default. After the accomplishment of docking simulations, conformations with negative binding energies were generated. The lowest binding energy conformer, i.e., pose of curcumin in the ligand-polymer complex was selected for the interpretation of various intermolecular interactions of curcumin with SE β-CD and estimation of binding affinity.

RESULTS AND DISCUSSION

In silico complexation studies of curcumin and SE β-CD [Figure 4] were performed using molecular docking simulations to investigate pre-formulation perspective to overcome bioavailability problems associated with curcumin. After the accomplishment of molecular docking simulations, the complexation affinity of curcumin with SE β-CD was obtained in the form of MolDock score [Table 1]. The Re-rank, H-bond, and Steric scores [Table 1] were also obtained as an output of molecular docking simulation runs. The accuracy of molecular docking simulations is improved by the Re-rank scoring function as it identifies the most probable docking solution after

execution of the molecular docking algorithm, and it is denoted by a weighted combination of the energy terms used by the MolDock score mixed with a few additional energy terms. MolDock score uses a piecewise linear potential for the estimation of the steric energy while re-rank score includes the steric (by LJ12-6) terms which are Lennard-Jones approximations to the steric energy. H-bond and Steric scores indicate the strength of H-bond and steric interactions, respectively, formed between curcumin and SE β-CD.

The binding affinity of curcumin was compared for both β-CD (MolDock Score - 189.144) and SE β-CD (MolDock Score - 223.404) [Table 1], and curcumin showed better binding affinity over β-CD. The Re-rank and steric scores of curcumin were good for SE β-CD (–176.837, –228.686, respectively) compared to β-CD (–151.668, –191.406, respectively). Curcumin showed prominent H-bond interactions (Bond Id. 1-5) with SE β-CD [Figure 5]. The electronegative atom oxygen present in both hydroxy the terminal hydroxy groups and one of the central ketone group is responsible for H-bond interactions with the polymer. The H-bond (Id. 4) was most strong (Bond energy –1.177 Kcal/mole Å) with bond length (3.365Å) [Table 2]. Curcumin exhibited good steric interactions (Bond Id. 1-3) with SE β-CD [Figure 6 and Table 3]. One of the terminal phenyl rings as well as the ketone group was involved in steric interactions with polymer.

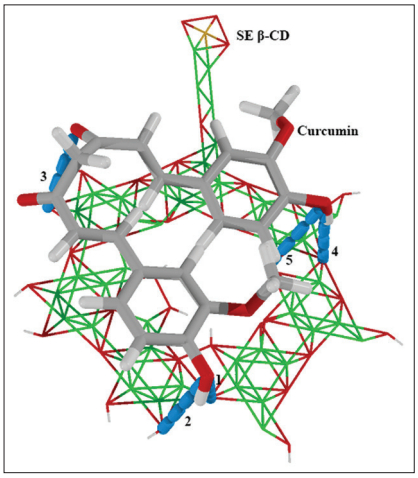

Figure 5: H-bond interactions (Id. 1-5, blue dotted bonds) of curcumin with sulfobutyl ether β-cyclodextrin

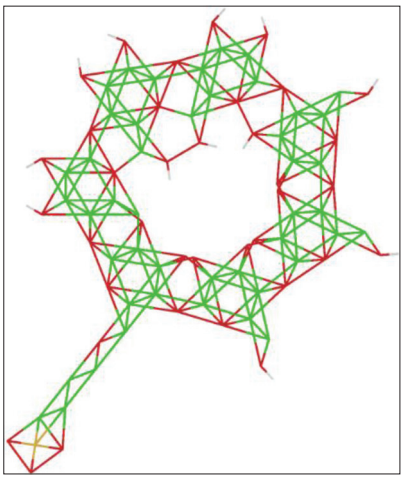

Figure 3: 3D-Structures of sulfobutyl ether β-cyclodextrin

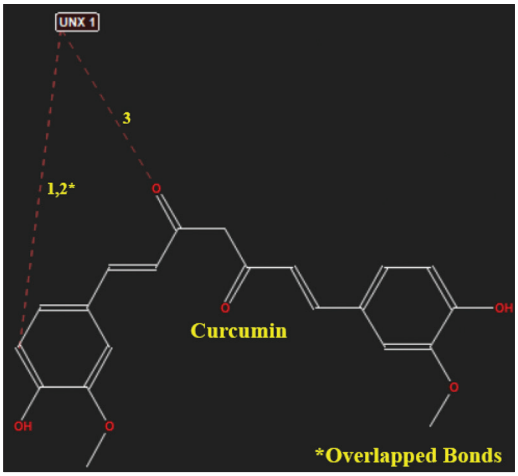

Figure 6: Steric interactions (id. 1-3, red dotted bonds) of curcumin with sulfobutyl ether β-cyclodextrin

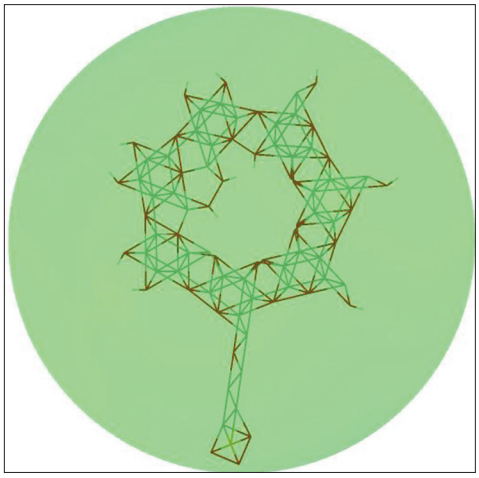

Figure 4: Search space setup for sulfobutyl ether β-cyclodextrin

Table 1: Docking scores of curcumin with β-CD and SE β-CD

Polymer Id.	Docking Scores (in Kcal/mol)			
	MolDock	Re-rank	H-Bond	Steric
β-CD	–189.144	–151.668	–5.897	–191.406
SE β-CD	–223.404	–176.837	–2.860	–228.686

CD: Cyclodextrin, SE: Sulfobutyl ether

Table 2: Properties of H-bond interactions (Id. 1-5) displayed by curcumin with SE β-CD

H-bond Id.	H-bond Donor	Energy (Kcal/mole Å)	Length (Å)
1	Ligand	–2.500	2.952
2	Either	–0.488	2.717
3	Polymer	–1.844	3.029
4	Ligand	–0.962	2.885
5	Ligand	–1.568	2.488

CD: Cyclodextrin, SE: Sulfobutyl ether

Table 3: Properties of Steric interactions (Id. 1–3) displayed by curcumin with SE β-CD

Steric bond Id.	Energy (Kcal/mole Å)	Length (Å)
1	0.860	3.160
2	0.870	3.160
3	0.730	3.180

CD: Cyclodextrin, SE: Sulfobutyl ether

CONCLUSION

The use of β-CDs for the formulation of host-guest complex is an optimum approach to enhance the solubility and in turn bioavailability of poorly soluble and bioavailable drugs and pharmaceutical substances. However, it is a tough task to choose the suitable polymer as it costly and time-consuming assignment to go in wet laboratory for hit and trial method. Computer-aided drug design tools provide a best solution for number of difficult tasks including toxicity and bioavailability problems associated with pharmaceuticals. Here, molecular docking simulations were used for the identification of best water-soluble β-CD, compared to conventional β-CD, for the preparation of curcumin formulations to overcome the poor bioavailability problem associated with it. *In silico* complexation studies were successfully performed for curcumin against polymer SE β-CD and compared with β-CD to investigate the pre-formulation perspective. The *in-silico* affinities and interaction studies showed that SE β-CD may be preferred over convention β-CD for the formulation purpose to overcome its bioavailability problems.

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