

# Salt and Cocrystals of Sildenafil with Dicarboxylic Acids: Solubility and Pharmacokinetic Advantage of the Glutarate Salt

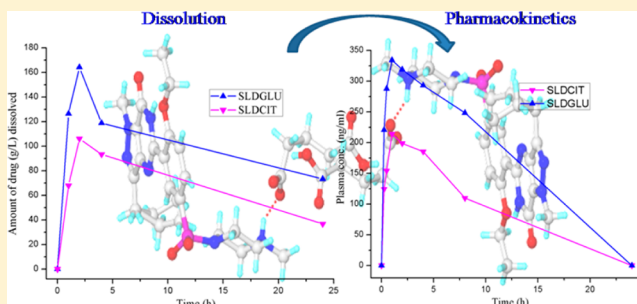
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## S Supporting Information

**ABSTRACT:** Sildenafil is a drug used to treat erectile dysfunction and pulmonary arterial hypertension. Because of poor aqueous solubility of the drug, the citrate salt, with improved solubility and pharmacokinetics, has been marketed. However, the citrate salt requires an hour to reach its peak plasma concentration. Thus, to improve solubility and bioavailability characteristics, cocrystals and salts of the drug have been prepared by treating aliphatic dicarboxylic acids with sildenafil; the *N*-methylated piperazine of the drug molecule interacts with the carboxyl group of the acid to form a heterosynthon. Salts are formed with oxalic and fumaric acid; salt monoanions are formed with succinic and glutaric acid. Sildenafil forms cocrystals with longer chain dicarboxylic acids such as adipic, pimelic, suberic, and sebacic acids. Auxiliary stabilization via C–H...O interactions is also present in these cocrystals and salts. Solubility experiments of sildenafil cocrystal/salts were carried out in 0.1N HCl aqueous medium and compared with the solubility of the citrate salt. The glutarate salt and pimelic acid cocrystal dissolve faster than the citrate salt in a two hour dissolution experiment. The glutarate salt exhibits improved solubility (3.2-fold) compared to the citrate salt in water. Solubilities of the binary salts follow an inverse correlation with their melting points, while the solubilities of the cocrystals follow solubilities of the coformer. Pharmacokinetic studies on rats showed that the glutarate salt exhibits doubled plasma AUC values in a single dose within an hour compared to the citrate salt. The high solubility of glutaric acid, in part originating from the strained conformation of the molecule and its high permeability, may be the reason for higher plasma levels of the drug.

**KEYWORDS:** bioavailability, dissolution, crystal engineering, X-ray crystallography, hydrogen bond



## INTRODUCTION

Drug molecules, active pharmaceutical ingredients (API), can exist in different solid forms such as polymorphs, amorphous phases, cocrystals, salts, and hydrate/solvates without changing their intrinsic chemical structures.<sup>1–4</sup> Each solid form is known to exhibit different physicochemical properties, and this is often determined by structural parameters.<sup>5–9</sup> A clear understanding of intermolecular interactions between the molecules in the solid state, in terms of their geometry and energy is crucial in the design of new pharmaceutical solid forms. These fundamental principles of crystal engineering find a ready application in the development of new solid state forms of APIs. To improve the solubility of a drug, a viable approach is the development of the salt form, provided the API has ionizable acidic/basic functional groups. Salt forms are well-known in the pharmaceutical industry and can improve solubility by almost 100–1000 fold when compared to the parent API.<sup>10–14</sup> Salts can, however, be hygroscopic. To counter the hygroscopicity problems of salts, cocrystals are an alternate option as they are stable and can also improve solubility to levels that are comparable to the amorphous phase.<sup>5,15–17</sup> Recently the US FDA identified pharmaceutical cocrystals as a promising solid dosage form because of their significance in pharmaceutical properties improvement. The US

FDA indicated that the cocrystals have to dissociate completely from the dosage form before reaching the target site of action.<sup>18</sup>

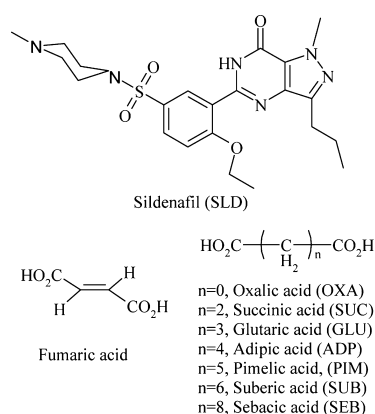
Sildenafil (SLD) (Scheme 1) is an inhibitor of cyclic GMP phosphodiesterase and was initially marketed as an anti-hypertensive agent (Brand name Revatio) by Pfizer (UK). The drug (Brand name Viagra) is now used mainly for the treatment of erectile dysfunction in elderly patients.<sup>19–21</sup> The parent API is a potent selective inhibitor of the enzyme phosphodiesterase (PDE-5). It destroys cyclic guanosine monophosphate (cGMP) and dilates blood vessels in the body. Due to its poor aqueous solubility (~5–10 mg/L), sildenafil exhibits incomplete absorption, has low bioavailability, and leads to slow onset of action. The API has been marketed as the citrate salt hydrate in 20–100 mg tablets for oral administration. In 2011 sales of Viagra exceeded \$2 billion worldwide. However, the citrate salt exhibits moderate solubility (3.5 g/L) and bioavailability (40%) and has a half-life of 3–4 h. It requires approximate 1 h to reach its peak plasma concentration because of its moderate solubility, and

**Received:** August 28, 2013

**Revised:** October 25, 2013

**Accepted:** October 29, 2013

**Published:** October 29, 2013

**Scheme 1. Chemical Structures of Sildenafil and Its Coformers**

this may be a problem for patients with cardiopulmonary diseases. However, the hydrate is not preferred as a solid dose formulation because of the stability issue and low solubility as compared to the anhydrous form.<sup>22–24</sup> Further, sildenafil citrate has a bitter taste, and hence tablets are commercially available as films coated with artificial sweeteners. Although this blockbuster drug has been in the news for over a decade, relatively little work has been done on the structural aspects and on its solubility and pharmacokinetic aspects.

The crystal structures of sildenafil citrate monohydrate<sup>25</sup> and solvates of the 1:1 saccharinate salt<sup>26</sup> are reported in the literature. A recent patent<sup>27</sup> has disclosed a drug–drug cocrystal of sildenafil with aspirin with improved solubility of the cocrystal compared to the API in 0.1N HCl medium. Another patent<sup>28</sup> has disclosed a few salt polymorphs of sildenafil with hydrochloric acid, sulfuric acid, ethanesulfonic acid, tartaric acid, and fumaric acid along with their solubilities, and these are compared to the sildenafil free base. Sawatdee et al.<sup>29</sup> reported a cyclodextrin nanosuspension of the citrate salt with improved solubility.

In a search for new solid forms with improved solubility and bioavailability compared to the citrate salt form, both the cocrystals and the salts have been screened in this study using pharmaceutically acceptable dicarboxylic acids. Succinic and adipic acids are included in the US FDA approved GRAS

(generally regarded as safe molecules) list.<sup>30</sup> Glutaric acid is a natural component of dietary foodstuffs and is a well-known metabolic intermediate of fatty acids metabolism. Pimelic acid derivatives are used in lysine biosynthesis.<sup>31</sup> Recently there have been a few reports on pharmaceutical cocrystal/salts of fluconazole,<sup>32</sup> pyrimethamine,<sup>33</sup> praziquantel,<sup>34</sup> and temozolomide<sup>35</sup> with dicarboxylic acids with improved solubility and stability. Chemical structures of the sildenafil and coformers are displayed in Scheme 1. The cocrystals and salts are characterized by Fourier transform infrared (FT-IR), differential scanning calorimetry (DSC), and powder and last single crystal X-ray diffraction. Here, we present structural aspects, hydrogen bonding, solubility, and pharmacokinetic behavior of sildenafil salts and cocrystals.

## RESULTS AND DISCUSSION

Stepanovs et al.<sup>36</sup> have recently reported the crystal structure of sildenafil. The API forms salts with both citric acid and saccharin.<sup>25,26</sup> Our attempt to cocrystallize saccharin with sildenafil citrate (to decrease bitterness of the API) proved unsuccessful. On the other hand, the product obtained was sildenafil citrate monohydrate (mostly) and sildenafil saccharinate acetonitrile solvate. In this work, aliphatic dicarboxylic acids were ground with the citrate salt using solvent drop assisted grinding. Stronger acids such as oxalic and fumaric acids form sildenafil oxalate and fumarate salts by replacing citric acid. Other long chain dicarboxylic acids did not produce the same results, and this may be because of weaker acidity. However, all of the coformers easily form cocrystals or salts with the free base sildenafil. The experimental conditions of the competitive supramolecular reactions are summarized in Table 1.

Sildenafil<sup>36</sup> contains a *N*-methylpiperazine fragment, and the N atom (attached to Me group) is the most basic site ( $\text{p}K_a = 8.7$ ) and least hindered to form a hydrogen bond (in cocrystal) or ionic bond (in salt). Based on the hydrogen bonding possibilities of the API, dicarboxylic acids were selected to obtain robust O–H...N heterosynthons<sup>37–39</sup> in the cocrystals. Oxalic acid ( $\text{p}K_a = 1.2$ ) and fumaric acid ( $\text{p}K_a = 3.0$ ) form salts, but weaker acids such as succinic acid ( $\text{p}K_a = 4.2$ ) and glutaric acid ( $\text{p}K_a = 4.3$ ) produce salt mono anions. Comparatively, long chain acids such as adipic acid ( $\text{p}K_a = 4.4$ ), pimelic acid

**Table 1. Experiments Attempted to Make Cocrystals of Sildenafil Citrate or Sildenafil**

	coformers attempted/crystallization	crystals obtained
sildenafil citrate	saccharin/MeOH	sildenafil citrate monohydrate
	saccharin/CH <sub>3</sub> CN	sildenafil saccharinate CH <sub>3</sub> CN solvate (1:1:1)
	oxalic acid	sildenafil oxalate (1:0.5)
	succinic acid/CH <sub>3</sub> CN	sildenafil citrate monohydrate
	fumaric acid/CH <sub>3</sub> CN, EtOH, THF	sildenafil citrate monohydrate
	fumaric acid/CH <sub>3</sub> OH	sildenafil fumarate trihydrate (1:1:3)
	glutaric acid/CH <sub>3</sub> CN	sildenafil citrate monohydrate
	pimelic acid/MeOH	sildenafil citrate monohydrate
sildenafil	oxalic acid/MeOH	sildenafil oxalate (1:0.5) salt
	fumaric acid/MeOH	sildenafil fumarate trihydrate (1:1:3)
	succinic acid/MeOH	sildenafil succinate (1:1)
	glutaric acid/MeOH	sildenafil glutarate (1:0.5)
	adipic acid/MeOH	sildenafil adipic acid (1:0.5)
	pimelic acid/MeOH	sildenafil pimelic acid (1:0.5)
	suberic acid/MeOH	sildenafil suberic acid (1:0.5)
	sebacic acid/MeOH	sildenafil sebacic acid (1:0.5)

Table 2. Crystallographic Parameters of Sildenafil and Its Cocrystal/Salts

	SLD-OXA	SLD-FUM	SLD-SUC	SLD-GLU	SLD-ADP
emp. formula	$C_{22}H_{31}N_6O_4S \cdot 0.5(C_2O_4)$	$C_{22}H_{31}N_6O_4S \cdot C_4H_3O_4 \cdot 3(H_2O)$	$C_{22}H_{31}N_6O_4S \cdot C_4H_3O_4$	$C_{22}H_{31}N_6O_4S \cdot 0.5(C_5H_6O_4)$	$C_{22}H_{31}N_6O_4S \cdot 0.5(C_6H_{10}O_4)$
formula wt	519.60	644.70	550.61	541.14	547.65
crystal system	triclinic	triclinic	monoclinic	monoclinic	monoclinic
space group	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P2_1/c$	$P2_1/c$
<i>T</i> (K)	150(2)	150(2)	150(2)	150(2)	150(2)
<i>a</i> (Å)	7.965(6)	11.714(3)	19.17(3)	19.850(6)	19.156(3)
<i>b</i> (Å)	12.445(9)	11.894(3)	15.05(3)	14.604(3)	14.846(2)
<i>c</i> (Å)	13.466(9)	13.531(3)	9.862(18)	9.684(4)	9.7216(15)
$\alpha$ (deg)	80.89(3)	101.666(9)	90	90	90
$\beta$ (deg)	75.26(2)	102.8040(10)	104.26(2)	100.608(13)	100.186(9)
$\gamma$ (deg)	77.71(2)	116.260(5)	90	90	90
volume (Å <sup>3</sup> )	1253.5(15)	1548.3(7)	2757(8)	2759.4(15)	2721.1(7)
<i>D</i> <sub>calcd</sub> (g cm <sup>−3</sup> )	1.377	1.383	1.326	1.318	1.337
<i>Z</i>	2	2	4	4	4
2 $\theta$ range	2.8–27.5	2.0–27.5	2.5–27.5	2.5–27.5	2.2–27.5
<i>R</i> <sub>1</sub> ( <i>I</i> > 2 $\sigma$ ( <i>I</i> )), <i>wR</i> <sub>2</sub>	0.0555, 0.1850	0.0516, 0.1718	0.0903, 0.2796	0.0955, 0.2807	0.0545, 0.1584
GOF	1.121	1.139	1.099	1.100	1.079
diffractometer	Rigaku-CCD	Rigaku-CCD	Rigaku-CCD	Rigaku-CCD	Rigaku-CCD
	SLD-PIM	SLD-SUB	SLD-SEB	NBA-GLU	
emp. formula	$C_{22}H_{31}N_6O_4S \cdot 0.5(C_7H_{12}O_4)$	$C_{22}H_{31}N_6O_4S \cdot 0.5(C_8H_{14}O_4)$	$C_{22}H_{31}N_6O_4S \cdot 0.5(C_{10}H_{18}O_4)$	$2(C_7H_6N_2O_3) \cdot C_3H_8O_4$	
formula wt	548.61	561.68	575.70	464.23	
crystal system	monoclinic	monoclinic	monoclinic	triclinic	
space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P\bar{1}$	
<i>T</i> (K)	130(2)	150(2)	150(2)	150(2)	
<i>a</i> (Å)	19.062(5)	19.031(10)	18.969(8)	7.0274(14)	
<i>b</i> (Å)	14.864(4)	15.097(7)	14.820(6)	11.049(2)	
<i>c</i> (Å)	9.925(3)	9.915(5)	10.525(4)	13.875(3)	
$\alpha$ (deg)	90	90	90	72.431(5)	
$\beta$ (deg)	100.889(15)	104.746(4)	99.559(17)	78.479(5)	
$\gamma$ (deg)	90	90	90	87.944(6)	
volume (Å <sup>3</sup> )	2761.6(13)	2755(2)	2918(2)	1006.0(3)	
<i>D</i> <sub>calcd</sub> (g cm <sup>−3</sup> )	1.320	1.354	1.311	1.532	
<i>Z</i>	4	4	4	2	
2 $\theta$ range	1.7–27.5	1.7–27.5	1.8–27.5	3.1–27.6	
<i>R</i> <sub>1</sub> ( <i>I</i> > 2 $\sigma$ ( <i>I</i> )), <i>wR</i> <sub>2</sub>	0.0570, 0.1853	0.0480, 0.1563	0.0977, 0.2804	0.0682, 0.1745	
GOF	1.148	1.131	1.188	1.018	
diffractometer	Rigaku-CCD	Rigaku-CCD	Rigaku-CCD	Rigaku-CCD	

( $pK_a = 4.5$ ), suberic acid ( $pK_a = 4.6$ ), and sebacic acid ( $pK_a = 4.7$ ) form cocrystals with sildenafil. Except the fumarate salt trihydrate (1:1:3) and the succinate salt (1:1), other multi-component systems maintain a 1:0.5 stoichiometry. Crystallographic parameters and normalized hydrogen bonds for the cocrystal/salts of sildenafil are summarized in Tables 2 and 3.

**Sildenafil Oxalate Salt (SLD-OXA, 1:0.5).** The crystal structure ( $P\bar{1}$ ,  $Z = 2$ ) contains a half equivalent of oxalate anion which is located on a crystallographic inversion center. Proton transfer from oxalic acid to the *N*-methylated piperazine ring of sildenafil confirms salt formation. The NH proton forms bifurcated hydrogen bonds with two oxalates through  $N^+ \cdots H \cdots O^-$  ionic interactions ( $N1-H1 \cdots O5$ : 1.60 Å, 161°;  $N1-H1 \cdots O6$ : 2.46 Å, 113°); see Figure 1a. Sildenafil molecules form dimers through auxiliary  $C-H \cdots O$  hydrogen bonds and connect to the next dimer via the oxalate anion (Figure 1b).

**Sildenafil Fumarate Salt Trihydrate (SLD-FUM, 1:1:3).** The salt ( $P\bar{1}$ ,  $Z = 2$ ) consists of one sildenafil cation, two half equivalent fumarate anions binding through one common hydrogen atom, and three water molecules. Proton transfer from fumaric acid to *N*-methylpiperazine fragment ( $N2^+ \cdots$

$H2N \cdots O7^-$ : 1.75 Å, 158°) confirms the ionic nature of the fumarate salt (Figure 2a). Fumarate monoanions form 1D chains along the crystallographic *b*-axis. Two asymmetric water molecules form a hydrogen bonded tetramer<sup>40,41</sup> via  $O-H \cdots O$  hydrogen bonds ( $O9-H9A \cdots O10$ : 1.82 Å, 173°;  $O10-H10A \cdots O9$ : 1.85 Å, 173°), whereas the third water molecule forms a hydrogen bond ( $O11-H11B \cdots O4$ : 1.78 Å, 170°) with the API carbonyl. Sildenafil molecules form a cavity in which fumarate anions (chain) sit in a channel along the crystallographic *b*-axis (Figure 2b).

**Sildenafil-Succinate (SLD-SUC, 1:1) and Sildenafil-Glutarate Salts (SLD-GLU, 1:0.5).** In the crystal structures of the salts of succinic and glutaric acid ( $P2_1/c$ ,  $Z = 4$ ), the dicarboxylic acids show positional static disorder in the internal carbon atoms at 150 K. An inversion center is present in the special position intersecting the carboxylate ions in succinic acid; see Figure 3a. The site occupancy factors (SOF) for internal carbons are therefore 0.5 each. We were unable to model the uncommon disorder in succinic acid precisely. It is difficult to conclude whether SLD-SUC is a cocrystal or salt as the CO bond distances are 1.21 and 1.23 Å. The FT-IR

Table 3. Hydrogen Bond Geometrical Parameters of Crystal Structures (O–H, N–H, and C–H Distances Are Neutron Normalized)<sup>a</sup>

compound	interaction	H...A (Å)	D...A (Å)	∠D–H...A (deg)	symmetry
SLD–OXA	N1–H1...O5	1.60	2.576(3)	161	–1 + x, y, z
	N1–H1...O6	2.46	3.000(3)	113	–x, 1 – y, 1 – z
	N4–H4...O3	1.86	2.666(3)	134	intramolecular
	C2–H2B...O1	2.51	3.516(3)	153	–x, –y, 1 – z
	C3–H3A...O2	2.46	2.924(3)	105	intramolecular
	C3–H3B...O4	2.31	3.366(3)	164	–x, 1 – y, –z
	C4–H4A...O2	2.57	3.561(3)	155	–x, –y, 1 – z
	C4–H4B...O6	2.36	3.012(3)	117	–x, 1 – y, 1 – z
	C5–H5B...O1	2.45	2.923(3)	105	intramolecular
	C7–H7...O5	2.26	3.176(3)	141	1 – x, 1 – y, 1 – z
	C11–H11...O2	2.50	2.915(3)	101	intramolecular
SLD–FUM	N2–H2N...O7	1.75	2.683(3)	158	2 – x, 1 – y, 1 – z
	N4–H4...O3	1.98	2.650(3)	123	intramolecular
	O9–H9A...O10	1.82	2.742(3)	173	–1 + x, –1 + y, z
	O9–H9B...O2	1.86	2.856(3)	174	1 – x, –y, –z
	O10–H10A...O9	1.85	2.787(3)	173	1 – x, 1 – y, –z
	O11–H11B...O9	1.86	2.888(3)	175	1 – x, –y, 1 – z
	O11–H11B...O4	1.78	2.805(3)	170	x, y, z
SLD–ADP	O6–H6...N1	1.65	2.635(2)	174	x, 1/2 – y, 1/2 + z
	N4–H4...O3	1.85	2.629(2)	131	intramolecular
	C3–H3B...O1	2.51	2.959(3)	104	intramolecular
	C4–H4A...O2	2.39	2.895(3)	106	intramolecular
	C13–H13C...O2	2.44	3.339(3)	140	–x, –y, 1 – z
	C2–H2B...O5	2.56	3.349(3)	131	1 – x, 1 – y, 1 – z
	C8–H8...O4	2.25	3.330(3)	172	x, 1/2 – y, –1/2 + z
SLD–PIM	O5–H5...N1	1.62	2.629(3)	174	1 – x, 1 – y, 2 – z
	N4–H4...O3	1.86	2.632(3)	136	intramolecular
	C8–H8...O4	2.54	3.537(4)	172	2 – x, –1/2 + y, 3/2 – z
	C12–H12A...O4	2.55	3.203(4)	117	2 – x, –1/2 + y, 3/2 – z
	C13–H13B...O1	2.50	3.361(3)	144	2 – x, –y, 1 – z
	N3–H3...O3	1.83	2.629(2)	133	intramolecular
SLD–SUB	O5–H5...N1	1.67	2.653(2)	173	x, 1/2 – y, –1/2 + z
	C3–H3A...O1	2.42	2.867(3)	103	intramolecular
	C4–H4B...O2	2.54	2.982(3)	103	intramolecular
	C8–H8...O4	2.34	3.420(3)	178	–x, –1/2 + y, 1/2 – z
	C11–H11...O2	2.53	2.923(3)	100	intramolecular
	C13–H13B...O1	2.41	3.402(3)	152	–x, 1 – y, –z
	N4–H4...O3	1.84	2.606(4)	141	intramolecular
SLD–SEB	O6–H6A...N1	1.78	2.642(5)	166	1 – x, 1 – y, 2 – z
	C3–H3A...O2	2.41	2.868(6)	104	intramolecular
	C7–H7...O1	2.51	2.910(6)	101	intramolecular
	C10–H10...O4	2.40	3.468(7)	169	–x, –1/2 + y, 1/2 – z
	C3–H13...O2	2.44	3.385(6)	145	–x, 1 – y, –z
	C24–H24B...O1	2.32	3.285(7)	148	x, y, 1 + z

<sup>a</sup>Note that H-bond parameters for succinate and glutarate salt are not added because of a disorder issue.

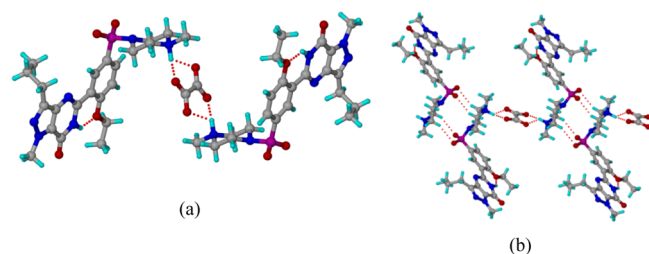
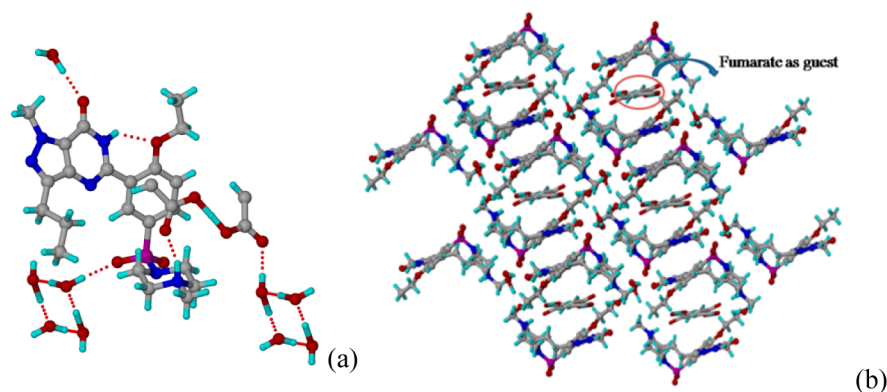


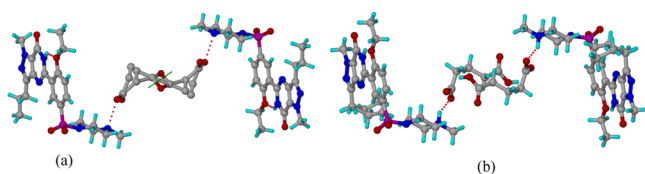
Figure 1. (a) Hydrogen bonding of SLD–OXA salt (1:0.5). (b) Oxalate anions bridge between two C–H...O hydrogen bonded sildenafil dimers.

spectrum of SLD–SUC (discussed next) indicates the possibility of one neutral carboxylic acid and a carboxylate anion in the coformer. A hydrogen bond is expected between *N*-methylpiperazine and succinic acid. In the sildenafil–glutarate salt, two carboxylic acids are positionally disordered between two sildenafil molecules. Unlike in the succinate salt, proton specification is easier here (obtained by modeling glutaric acid). The four C–O bond distances in glutaric acid are 1.26, 1.28, 1.21, and 1.32 Å, and this suggests that the sildenafil glutarate salt exists as a salt monoanion (Figure 3b). The glutarate is present in a folded conformation compared to the usual extended zigzag chain.



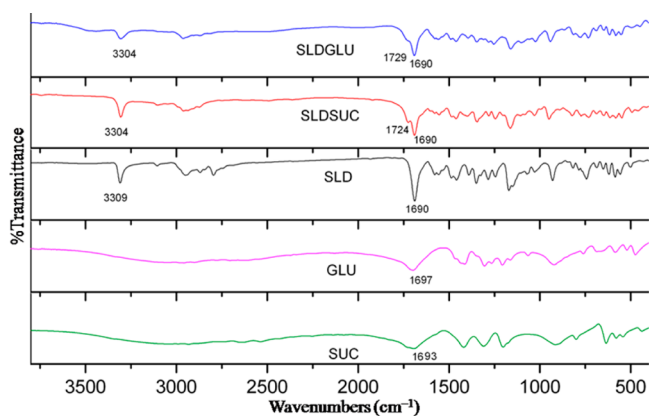


**Figure 2.** (a) Hydrogen bonding of SLD–FUM salt. (b) Fumarate anions act as guest inside (shown in circle) the cavity formed by the SLD cations.



**Figure 3.** (a) Hydrogen bonded tricomponent assembly between (a) two sildenafil and one succinate salt monoanion (disorder) and (b) glutarate salt monoanion.

Succinate and glutarate salt monoanions were further confirmed by FT-IR spectroscopy. The sildenafil molecule contains sulfone, amide carbonyl, and ring NH groups. The API exhibits vibrational bands at  $1166\text{ cm}^{-1}$  ( $\text{SO}_2$  symmetric),  $1356\text{ cm}^{-1}$  ( $\text{SO}_2$  asymmetric),  $1690\text{ cm}^{-1}$  ( $\text{C}=\text{O}$  asym), and  $3309\text{ cm}^{-1}$  (NH stretch) in the vibrational spectra. For SLD–SUC and SLD–GLU, there are  $\text{C}=\text{O}$  bands at  $1724$  and  $1729\text{ cm}^{-1}$  (blue shift from cocrformers), which indicates salts, not cocrystals (Figure 4). However, in the salts, there are no IR bands at  $1920$

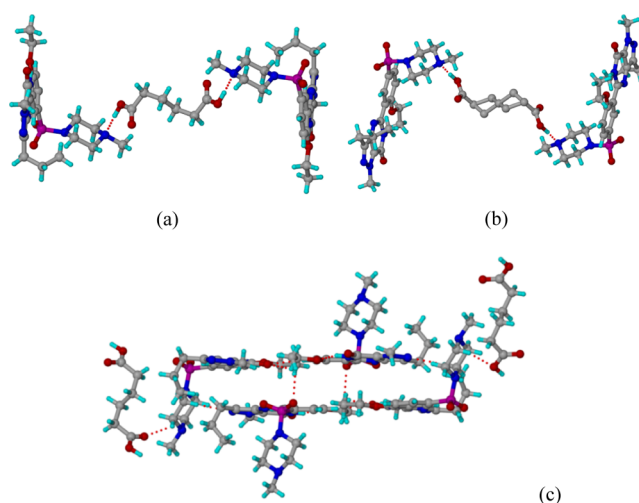


**Figure 4.** FT-IR vibrational frequency comparison between SLD–SUC and SLD–GLU salts.

and  $2450\text{ cm}^{-1}$  which corresponds to the acid–piperazine heterosynthon present in SLD cocrystals (Figure S4, ESI). But as SLD–GLU is a salt monoanion (confirmed from the crystal structure), we can expect the same for SLD–SUC salt because of the similarity of  $\text{C}=\text{O}$  bands.

**Sildenafil–Adipic and Sildenafil–Pimelic Acid Cocrystals (SLD–ADP, SLD–PIM, 1:0.5).** The cocrystals ( $P2_1/c$ ,  $Z = 4$ ) consist of  $\text{O}–\text{H}\cdots\text{N}$  hydrogen bonds ( $\text{O6}–\text{H6}\cdots\text{N1}$ :  $1.65\text{ Å}$ ,  $174^\circ$ ,  $\text{O5}–\text{H5}\cdots\text{N1}$ :  $1.62\text{ Å}$ ,  $174^\circ$ ) involving dicarboxylic acid

and *N*-methylpiperazine of the API, see Figure 5a, b). Sildenafil molecules interact with adipic acid through  $\text{C}–\text{H}\cdots\text{O}$

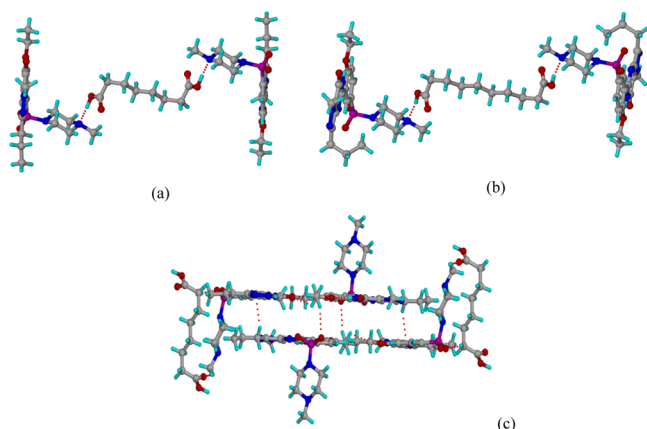


**Figure 5.** Common  $\text{O}–\text{H}\cdots\text{N}$  hydrogen bonding motif in (a) SLD–ADP and (b) SLD–PIM cocrystals. (c)  $\text{C}–\text{H}\cdots\text{O}$  hydrogen bonds between SLD and carboxylic acid in SLD–ADP cocrystal.

interactions ( $d$ ,  $2.56\text{ Å}$ ;  $\theta$ ,  $131^\circ$ ) between the aliphatic  $\text{CH}_2$  of piperazine ring of SLD with the carbonyl of the acid. In the SLD–ADP cocrystal, four sildenafil molecules form tetramers through auxiliary  $\text{C}–\text{H}\cdots\text{N}$  and  $\text{C}–\text{H}\cdots\text{O}$  interactions (Figure 5c). A similar packing motif is also present in the SLD–PIM cocrystal. There is a positional disorder of C25 carbon atom (SOF 0.6 and 0.4) in pimelic acid. An inversion center intersects pimelic acid from the middle carbon C26 with equal SOF's each of 0.5.

**Sildenafil–Suberic and Sildenafil–Sebacic Acid Cocrystals (SLD–SUB, SLD–SEB, 1:0.5).** The cocrystals ( $P2_1/c$ ,  $Z = 4$ ) consist of the common hydrogen bonding motif of  $\text{O}–\text{H}\cdots\text{N}$  interaction ( $\text{O5}–\text{H5}\cdots\text{N1}$ :  $1.67\text{ Å}$ ,  $173^\circ$ ,  $\text{O6}–\text{H6A}\cdots\text{N1}$ :  $1.78\text{ Å}$ ,  $166^\circ$ ) between carboxylic acid and *N*-methyl piperazine of the API which results in a tricomponent assembly (Figure 6a, b). In the suberic acid cocrystal, four sildenafil molecules form a tetramer through  $\text{C}–\text{H}\cdots\text{O}$  and  $\text{C}–\text{H}\cdots\pi$  interactions and interact with carbonyl acceptor of the dicarboxylic acid (Figure 6c). A similar hydrogen bonding motif is also present in the sebacic acid cocrystal.

It is interesting to note that SLD cocrystals with adipic to sebacic acid have similar cell parameters (Table 2), even though there is a variation in alkyl chain length in the dicarboxylic



**Figure 6.** Common O–H...N hydrogen bonding motif in (a) SLD–SUB and (b) SLD–SEB cocrystals. (c) C–H...O hydrogen bonds between sildenafil and carboxylic acid in SLD–SUB cocrystals.

acids. It may be possible that the zigzag alkyl chain of dicarboxylic acids occupy the space between the two APIs. Further, positional disorder is present in the corresponding salts/cocrystals with the coformer dicarboxylic acids, for example, succinic (even,  $n = 2$ ), glutaric (odd,  $n = 3$ ), and pimelic acid (odd,  $n = 5$ ), because the cofomers may not fit properly in the available space between two SLD molecules. Moreover, odd dicarboxylic acids are present in a disordered structure possibly because of their high energy conformations and strained trapezoid geometry. There may be certain optimum distance required between the two API's to form a tricomponent assembly. Here adipic acid ( $n = 4$ ) has the optimum chain length required to avoid steric repulsion between the two API molecules. All of the new solid forms were further characterized by FT-IR, PXRD, and DSC; see the Supporting Information.

**Solubility and Stability Study.** The solubility of sildenafil is pH-dependent and decreases with increase of pH of the medium.<sup>42</sup> All of the solubility experiments were carried out in 0.1 N HCl medium at 4 and 24 h to examine the effect of acidic pH (see Table 4). The apparent solubility of sildenafil after 4 h

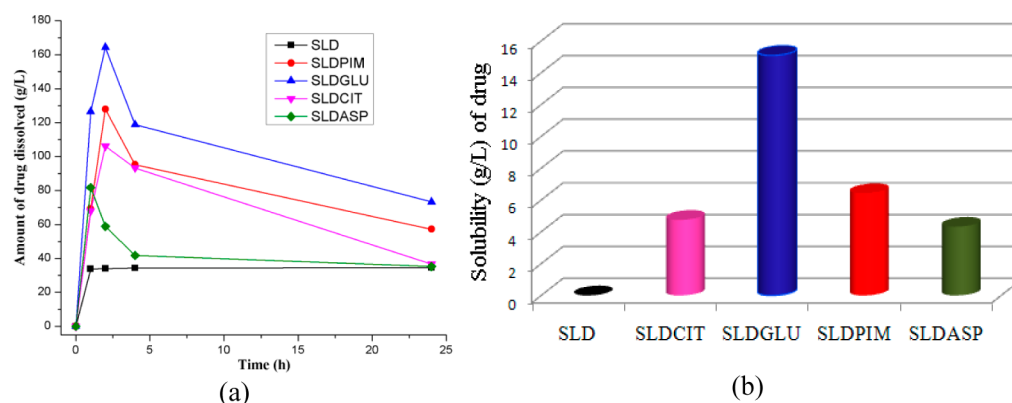
was 34.3 g/L, which is the solubility of sildenafil hydrochloride hydrate (SLD–HCL). SLD–HCL exhibits a characteristic peak at  $6.7 \pm 0.2^\circ 2\theta$  (see Figure S5a, SI), which is prominent in all of the solid forms after 4 h of the solubility experiment. At 4 h, the solubility of the SLD–CIT salt was 93.3 g/L. However, after 24 h, the solubility of the citrate salt decreased to 36.7 g/L. This happens because of a phase transformation of SLD–CIT to SLD–HCL. Among all of the binary systems, SLD–OXA showed the lowest solubility of 8.5 g/L and transformed to SLD–HCL within 4 h. In comparison, the SLD–FUM salt is stable up to 4 h in a slurry experiment, and the solubility increased from 32.3 g/L (4 h) to 47.4 g/L (24 h). As expected, sildenafil citrate exhibits a higher solubility than the oxalate and fumarate salts because of higher solubility of the citric acid. Comparatively, SLD–SUC salt exhibits moderate solubility (74 g/L). The SLD–GLU salt showed the highest solubility of 119 g/L at 4 h. Further, the SLD–GLU salt showed the highest solubility (164 g/L) at 2 h, which is more than the SLD–CIT salt hydrate (106 g/L, 2 h) (Figure 7a).

The solubility of a binary system may be affected by the factors such as interactions in the crystal lattice, melting point (mp), solubility of the coformer, and finally particle morphology. Let us consider these factors in turn: considering the bond distances between the API and coformer, the interaction between sildenafil cation and oxalate anion is the strongest ( $N^+ - H \cdots O^-$ ,  $D$ , 2.57 Å), and hence the solubility of the oxalate salt is expected to be the least among the salts (Table 4). In the fumarate, glutarate, and citrate salts, longer hydrogen bond distances ( $D$ , 2.67, 2.69, and 2.68 Å) between the API and cofomers are observed, which correlates with their higher solubility compared to the oxalate salt. Considering the solubilities of the cofomers, the citrate salt showed a higher solubility than the oxalate and fumarate salt due to the higher solubility of citric acid. The oxalate salt should correspondingly have a higher solubility than the fumarate salt. However, this was not observed, and this also agrees with the higher melting point (m.p.) of the oxalate salt (Table S4). Also, there is an inverse correlation between mp and solubility of the SLD salts (Figure 8a). SLD–GLU salt has the lowest mp and the highest solubility among the SLD salts.

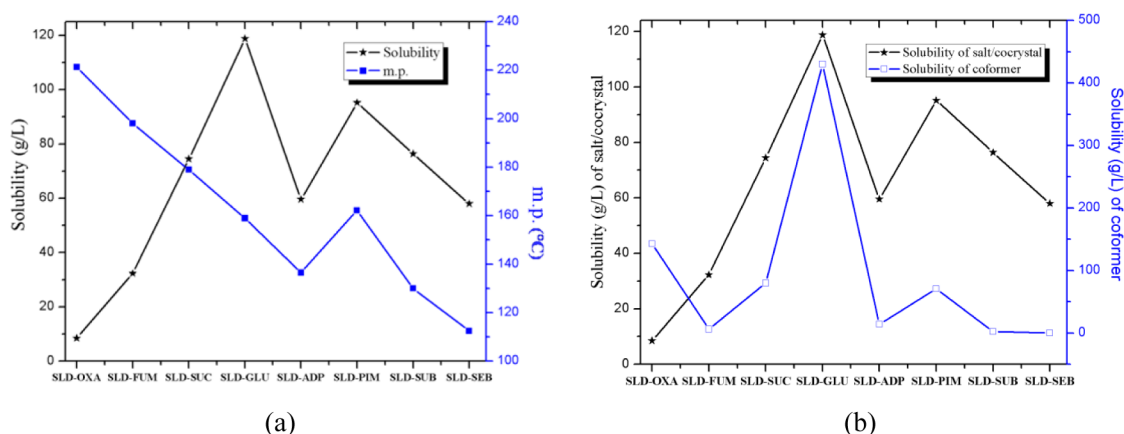
**Table 4.** Solubility Profiles of Sildenafil and Its New Solid Phases in 0.1N HCl Medium

crystalline forms	absorption coefficient ( $\text{mM}^{-1}\text{cm}^{-1}$ )	apparent solubility (g/L) at 4 h (2 h)	solubility (g/L) at 24 h	aqueous solubility (g/L) of cofomers <sup>a</sup>	distance, $D$ (Å), $N^+ - H \cdots O^- / O - H \cdots N$ (Å)	residue obtained after solubility expt. (4 h)
SLD	12.34	34.3	34.5			SLD + SLD–HCL
SLD–CIT	14.09	93.3 (106.1)	36.7	730	2.674, 2.911	SLD–CIT + SLD–HCL
SLD–OXA	11.40	8.5	7.6	143	2.574, 3.005	SLD–HCL + SLD–OXA
SLD–FUM	10.81	32.3	47.4	6.3	2.683	SLD–FUM
SLD–SUC	12.82	74.5	48.7	80	2.675	SLD–SUC + SLD–HCL
SLD–GLU	12.57	118.8 (164.3)	73.7	430	2.691	SLD–GLU + SLD–HCL
SLD–ADP	14.33	59.6	38.6	14	2.635	SLD–ADP + SLD–HCL
SLD–PIM	13.33	95.2 (127.9)	57.2	71	2.629	SLD–PIM + SLD–HCL
SLD–SUB	12.40	76.4	65.0	2.5	2.654	SLD–SUB + SLD–HCL
SLD–SEB	13.31	58.0	42.9	0.3	2.642	SLD–SEB + SLD–HCL

<sup>a</sup>Note: Solubility values of cofomers were obtained from literature.



**Figure 7.** (a) Dissolution studies of SLD, its salts, and cocrystals in 0.1 N HCl aqueous medium. (b) Solubility comparisons in water at 2 h of dissolution.



**Figure 8.** Solubilities (at 4h) of the SLD salt/cocrystals correlations with their (a) melting points (mp) and (b) the solubility of the coformers. Note that the inverse correlation between mp and solubility is valid for salts only. Except for oxalate salt, the solubility of other binary systems increases with the coformer solubility.

Finally, morphology may play a role in improving the dissolution rate of a solid form. Generally, block or plate morphologies provide higher surface area than an acicular morphology. This increases the exposure to the medium and hence the dissolution. In the present context, SLD-GLU has a thick plate morphology (single crystals) compared to the acicular citrate salt. This may be another reason for improved dissolution rate of the glutarate salt.

Considering the cocrystals, the SLD-PIM cocrystal showed the highest solubility of 128 g/L (after the glutarate salt) at 2 h of dissolution. The solubility of the cocrystals follows the same order as the solubility of the coformers<sup>15</sup> (Figure 8b). Generally, cocrystals having longer alkyl chains and formed from dicarboxylic acids (pimelic, suberic, sebacic acid) are more hydrophobic and hence exhibit poor aqueous solubility. SLD-SEB showed the least solubility (58.0 g/L) at 4 h of dissolution. The reported aspirin cocrystal<sup>27</sup> (SLD-ASP) showed a higher solubility of 82 g/L compared to the citrate salt at 1 h but transformed faster to the hydrochloride salt compared to the highly soluble SLD-GLU salt and SLD-PIM cocrystal (Figure S5, SI).

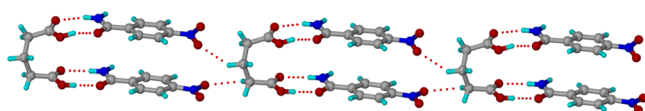
Another important aspect is that multicomponent systems with odd acids (glutaric, pimelic acid) showed higher solubility than their even counterparts (succinic, adipic, suberic). This could be because of the strained geometry and high energy and hence high solubility of the coformers.<sup>43,44</sup> Strained geometry is also reflected in the glutarate salt and pimelic acid cocrystal

structures. Glutarate salts showed higher solubility than the pimelic acid cocrystals in keeping with the solubilities of the carboxylic acids—GLU (430 g/L) is more soluble than PIM (71 g/L). The solubility experiment suggests that all of the solid forms (except SLD-FUM) transformed to SLD-HCL after 4 h in acidic medium. The stability of SLD-FUM salt (4 h) is due to the presence of three water molecules in the crystal lattice, and hence there is a natural tendency to exclude water molecules (external) during dissolution. However, after 24 h slurry experiments, all of the solid forms transformed to SLD-HCL as confirmed by PXRD comparisons (Figure S5, ESI).

The apparent solubility of SLD-CIT, SLD-GLU salts, and SLD-PIM, SLD-ASP cocrystals were carried out in distilled water (neutral pH) at 2 h. The solubility of the citrate salt is 4.7 g/L at  $37 \pm 1$  °C. SLD-GLU (solubility 15.1 g/L) and SLD-PIM (solubility 6.4 g/L) are 3.2 and 1.3 times more soluble than the citrate salt; see Figure 7b. However, the prior art SLD-ASP cocrystals<sup>27</sup> showed less solubility compared to the citrate salt. All of the solid phases are stable in water as seen after 2 h of solubility experiments, confirmed by the PXRD comparisons. The rates of phase transformation of all SLD cocrystals and salts to SLD-HCL are much faster in acidic medium than in neutral medium.

**Conformations of Glutaric Acid and the High Solubility.** The high solubility of glutaric acid containing salts can be explained by the possible occurrence of different conformations of the glutaric acid in solution. Drug solubility is

a function of molecular flexibility and/or polar surface area. Hence increased rotational degrees of freedom may often decrease crystallinity of the drug (solute), resulting in improved aqueous solubility and absorption.<sup>2,45</sup> In the case of cocrystals and salts of the highly soluble glutaric acid, both enthalpy and entropy play a role in their solubility. The coformer is more soluble than the API. During dissolution, it is reasonable that the coformer (here GLU) dissolves first, followed by the transformation of the API into a higher energy amorphous phase through rearrangement of molecules caused by the voids created by dissolution of the coformers.<sup>46,47</sup> The greater the solubility of the coformer, the faster the API could transform to the amorphous phase followed by supersaturation. An unusual bent (semicircle) conformation of glutaric acid in 4-nitrobenzamide–glutaric acid cocrystal was seen in our studies (NBA–GLU, Figure 9). This is the only conformation of



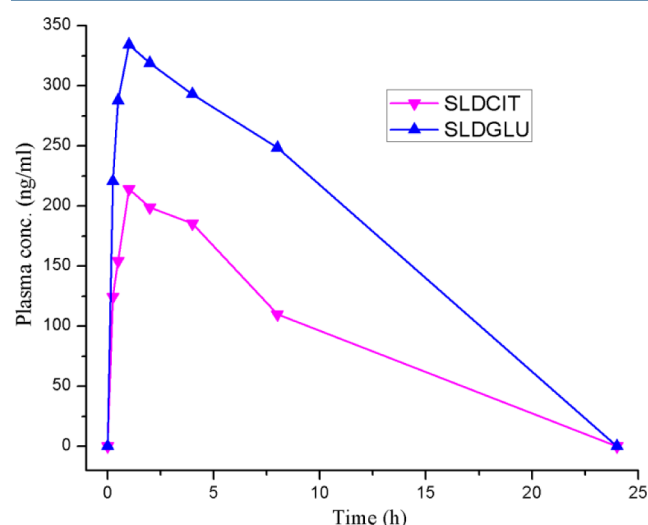
**Figure 9.** 4-Nitrobenzamide–glutaric acid (NBA–GLU, 2:1) cocrystal. Notice the bent (semicircle) conformation of glutaric acid connected to 4-nitrobenzamide via acid–amide synthons followed by auxiliary C–H...O interactions.

glutaric acid (enthalpy effect), where both the carboxylic acid groups are in the *syn* location because of acid–amide heterosynthon formation between a glutaric acid and two 4-nitrobenzamide molecules. The auxiliary C–H...O interactions between the CH<sub>2</sub> of GLU with the NO<sub>2</sub> group of the benzamide drives the bent conformation of the carboxylic acid. The energy difference between the flat (chain) and bent (semicircle) conformations is quite high (3.65 kcal/mol); see Table S1 and Figure S1, SI. The conformational energy of the observed GLU conformer in the SLD–GLU salt is 1 kcal/mol higher than the flat (chain) geometry. Among all of the aliphatic dicarboxylic acids (oxalic acid to sebacic acids), only GLU (*n* = 5) has the optimum chain length, suitable for a bent conformation. It can be hypothesized that when the higher energy GLU (partially bent) in salt dissolves in aqueous medium, the conformation of the GLU changes from the bent to flat geometry. During dissolution, the trapped water (more structured) in the bent conformer of GLU is expected to be pushed to the bulk water with entropy gain. This gain results in a lowering in free energy of the system and facilitates the dissolution process of SLD–GLU.

The solubility (2 h) ratio of NBA–GLU cocrystal and NBA is only 18, whereas the solubility ratio of SLD–GLU salt compared to SLD is very high (3020-fold). Of course salts can increase solubilities much more compared to cocrystals. Again, the aqueous solubility of NBA–GLU cocrystal (1.69 g/L), which is 1.3-fold more than the reported NBA–SUC (1.28 g/L) and NBA–ADP (1.25 g/L) cocrystals<sup>48</sup> after 30 min of dissolution, correlates with the solubility of the coformers themselves; the anomalous higher solubility of the glutaric acid salts and cocrystals may be the effect of high energy bent conformation of glutaric acid. Hence it is expected that, along with the higher energy conformation of glutaric acid, salt formation also contributes toward improving solubility. Again, the melting point and density of glutaric acid are the lowest and molar entropy is the highest in the series of malonic to pimelic acids.<sup>49,50</sup> The above unusual physical properties of glutaric acid

could well be the reason for higher solubility of the acid itself and of cocrystals and salts comprising the acid. However, compared to the citrate salt and pimelic acid cocrystal, glutarate salt follows the parachute model<sup>46,47</sup> by increasing the lifetime of the metastable states of the API, which is necessary for a stable drug formulation.

**Pharmacokinetic Study.** Oral bioavailability, the fraction of the oral dose that reaches the arterial blood in its active form, is an important physical property for drug formulation. Improving the solubility of a solid form by cocrystal/salts can have a dramatic impact on absorption and bioavailability<sup>16,51–53</sup> Thus, pharmacokinetic studies of the citrate and glutarate salts were carried out on male Sprague–Dawley rats. Oral bioavailability can be assessed by measuring AUC (area under the curve) or C<sub>max</sub> (peak plasma concentration). At a single administered dose of 5 mg/kg, glutarate salt showed a higher peak plasma concentration (334 ng/mL) compared to the citrate salt (214 ng/mL, Figure 10) within 1 h, while AUC<sub>0–24h</sub>



**Figure 10.** Mean plasma concentration–time profile of the citrate and glutarate salt in rats.

almost doubled for the glutarate salt. Further, glutarate salt showed improved shelf life of the drug more than twice compared to the citrate salt; see Table 5. Amidon and Löbenberg<sup>54</sup> in their models have shown that oral bioavailability is a product of permeability and solubility. To obtain high bioavailability, an increased level of solubility and permeability are required. Glutaric acid is a highly soluble and permeable dicarboxylic acid, which also correlates with the high bioavailability of the glutarate salt. By improving AUC values of the glutarate salt by a factor of 2, it is expected that the bioavailability of sildenafil will go up.

## CONCLUSIONS

Sildenafil is a well-known drug used to treat erectile dysfunction and pulmonary arterial hypertension but faces problems of poor aqueous solubility and bioavailability. To improve the solubility of the API, multicomponent molecular crystals were prepared through solvent assisted and slurry grinding methods. Among the new synthesized solid forms, oxalic and fumaric acids form salts with the API. However, the formation of cocrystals is more predominant with increasing carbon chain length (succinic acid to sebacic acid). Succinic and glutaric acids showed positional



**Table 5.** Mean Pharmacokinetic Parameters of Glutarate and Citrate Salts Following Oral Administration to Male Sprague–Dawley Rats

compound	route	dose (mg/kg)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	T <sub>1/2</sub> (h)	AUC <sub>0–24</sub> (ng·h/mL)
SLD–GLU	oral	5	334.10	1.0	15.06	4220
SLD–CIT	oral	5	214.01	1.0	6.70	2200

static disorder in the corresponding salt monoanions. There is a decrease in melting points with increasing chain length for the cocrystals/salts with even dicarboxylic acids, but the same trend is not observed in cocrystals/salts with the odd acids. Sildenafil–glutarate salt and sildenafil–pimelic acid cocrystal showed improved solubility and also inhibit phase transformation when compared to the citrate salt in 0.1 N HCl medium. The glutarate salt is more soluble than the citrate salt in water. The solubility of the API salts follows an inverse correlation with their melting points, while the cocrystals follow the solubility of the coformers. Cocrystals/salts with odd dicarboxylic acids showed better solubility than their even counterparts. An unusual bent conformation of glutaric acid was observed, which is relevant in demonstrating the crystallization pathway of glutaric acid from a bent to straight chain geometry and gives a possible reason for high solubility of the glutarate salt. Further, the glutarate salt exhibits increased plasma AUC and shelf life which is more than twice compared to the citrate salt. Hence sildenafil glutarate salt is a promising candidate for next stage of formulation development and can be an alternate solid form of the citrate salt.

## ■ EXPERIMENTAL SECTION

Sildenafil citrate salt was supplied by Ranbaxy Laboratories (Gurgaon, India). The free base was prepared by slurrying the citrate salt in 0.05 (M) NaOH solutions for 3–4 days. The free base sildenafil was crystallized from MeOH as parallelogram plate crystals, which is confirmed with the reported crystal structure.<sup>36</sup>

Sildenafil and aliphatic dicarboxylic acid coformers were taken in a definite stoichiometric ratio (preferably 1:1 or 1:0.5) and ground in a mortar-pestle for 15–30 min with a dropwise addition of MeCN, MeOH, or EtOH. The final mixture was characterized by FT-IR, PXRD, and DSC. Crystallization conditions of the cocrystal/salts preparation are summarized in Table S2.

4-Nitrobenzamide–glutaric acid (2:1) cocrystal. 4-Nitrobenzamide and glutaric acid were taken in a 2:1 molar ratio and ground after adding 2–3 drops of EtOH (solvent drop grinding). The ground sample was dissolved in a minimum amount of 1:1 mixture of CHCl<sub>3</sub> and MeOH in vial. Later, based on vapor diffusion method, the vial was kept in a CHCl<sub>3</sub> containing beaker. Good quality crystals were obtained after six days.

**Single Crystal X-ray Diffraction.** Single crystal X-ray data for all of the binary systems were collected on a Rigaku Mercury375/M CCD (XtaLAB mini) diffractometer using graphite monochromated Mo–K $\alpha$  radiation at 150 K. The data were processed with the Rigaku Crystal clear software.<sup>55</sup> Structure solution and refinements were executed using SHELX-97<sup>56</sup> using the WinGX<sup>57</sup> suite of programs. Refinement of coordinates and anisotropic thermal parameters of non-hydrogen atoms were performed with the full-matrix least-squares method. The different treatment of H in D–H in any structure depends on the data quality. All of the hydrogen atoms in NH, OH, and CH are located from difference Fourier

maps. PLATON<sup>58,59</sup> software was used to check correct symmetry. Disorder in glutarate and pimelic acid was modeled successfully, but there were problems with the succinate salt. X-Seed<sup>60</sup> was used to prepare the packing diagrams of the cocrystals and salts. Crystallographic CIF files (CCDC Nos. 956673–956681) are available at [http://www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif) or as part of the Supporting Information.

**Thermal Analysis.** DSC was performed on a Mettler Toledo DSC 822<sup>e</sup> module. About 4–6 mg of the sample was placed in crimped but vented aluminum pans of 40  $\mu$ L, and the temperature range scanned was 30–250 °C at a heating rate of 5 °C/min. The sample was purged by a stream of dry nitrogen flowing at 50 mL/min. DSC endotherms of the API and its cocrystals and salts are shown in Figure S2, SI. Melting points (°C) of the API, salts, and cocrystals are summarized in Table S4 (obtained from DSC data) and compared with the coformers. Similar to the reported sildenafil citrate and saccharinate salt,<sup>25,26</sup> oxalate and fumarate salts also melt at a temperature higher than the API, but all of the cocrystals melt lower than the API. There is a downward trend of melting points of cocrystal/salts of sildenafil (as coformers) with increasing alkyl chain length of even dicarboxylic acids. However, the same trend is not observed for odd carboxylic acid cocrystals and salts. A 1:1 ground mixture of sildenafil and succinic acid results a single endotherm at 179 °C, but same stoichiometry of the API and glutaric acid melts at 159 °C preceded by melting of glutaric acid (92–97 °C). The single endotherm of the API and glutaric acid (1:0.5) ground mixture in DSC further confirms the stoichiometry.

**Powder X-ray Diffraction.** Powder X-ray diffraction data were collected on a Philips X'pert Pro X-ray powder diffractometer equipped with X'cellerator detector. The scan range, step size, and time per step were  $2\theta = 5.0$  to  $40^\circ$ ,  $0.017^\circ$ , and 30 s, respectively. The formation of cocrystal/salt was monitored by the appearance of new diffraction lines using X'pert HighScore software. The bulk phase purity of the cocrystal/salts was confirmed from the comparison with the calculated lines obtained from single crystal X-ray data (Figure S3, SI). However, there are powder X-ray pattern differences ( $2\theta < 15^\circ$ ) between sildenafil succinate salt crystal structure and its bulk material obtained through MeOH solvent assisted grinding. This indicates a possibility of sildenafil succinate salt polymorphs<sup>24,61</sup> (see Figure S3d, SI).

**Vibrational Spectroscopy.** FT-IR spectra were recorded on samples dispersed in diffused reflectance mode in the range of  $4000\text{--}400\text{ cm}^{-1}$  in a Perkin-Elmer FTIR spectrometer. Data were analyzed using Spectrum software. IR bands at 1920 and  $2450\text{ cm}^{-1}$  represent acid–piperazine heterosynthon present in all of the cocrystals of adipic acid to sebacic acid. As expected those bands are absent in the oxalate to glutarate salts (Figure S4, SI). FT-IR vibrational frequencies ( $\text{cm}^{-1}$ ) of sildenafil and its multicomponent systems are summarized in Table S3.

**Solubility Study.** The absorption coefficient of each solid phase was measured from the slope of the absorbance vs concentration of the five known concentrated solutions in 0.1 N HCl aqueous medium and distilled water and measured at

293 nm in a Perkin-Elmer UV–vis spectrometer. The solubility of each solid was measured at 4 h and also 24 h using the shake-flask method.<sup>62</sup> For SLD, SLD–CIT, SLD–GLU, and SLD–PIM, apparent solubilities were measured at 1 and 2 h. Similarly, solubility experiments were carried out in water (neutral pH) at 2 h to observe the effect of pH on the SLD cocrystals and salts.

**Pharmacokinetic Study.** Pharmacokinetic data of the glutarate and citrate salts were evaluated in four healthy male Sprague–Dawley rats ( $n = 2$  per group, weighing 150–200 g) following oral administration of 5 mg/kg dose. Oral formulation prepared as a suspension using 0.25% w/v sodium carboxy methyl cellulose with 0.1% (w/v) Tween 80 in water was administered. A portion of 0.2 mL of blood samples was collected from the saphanous vein at 0, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h from each rat, immediately centrifuged for 10 min at 4000 rpm at  $4 \pm 2$  °C and stored below  $-70$  °C until the assay. Concentrations of the respective compounds in rat plasma samples were determined by a validated HPLC method. All pharmacokinetic parameters are reported as mean and standard deviations.

**Molecule Conformation Energy Calculation.** For molecules geometrical optimization, except bent glutaric acid, all of the glutaric acid molecules were directly taken from the Crystal Structure Database (CSD). The molecules geometrical optimization was carried out by B3LYP/6-311g (d, p) basis set using the Gaussian 03 package. See the Supporting Information for details.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

Conformational energy calculation, DSC, FT-IR, and PXRD of the cocrystals and salts. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We are thankful to Ranbaxy Pvt. Ltd. for providing the API sildenafil citrate. P.S. thanks Ranbaxy for a fellowship. S.T. thanks UGC for a SRF. S.G. thanks IISc for a fellowship. G.R.D. thanks DST for a J. C. Bose fellowship.

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