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Multicomponent Drug Crystals of Sildenafil: Salicylate and Salicylate Cocrystal with Salicylic Acid Sesquihydrate – Preparation and Crystal Structure

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I. INTRODUCTION

New multicomponent drug solids comprising sildenafil (**sil**) and salicylic acid (**sa**) were designed according to drug combination rational principles and prepared in crystalline form, namely, sildenafil salicylate (1:1) (**sil**⁺(**sa**)⁻) and sildenafil salicylate cocrystal with salicylic acid sesquihydrate (1:1:1.5) (**sil**⁺(**sa**)⁻(**sa**) (Scheme 1). Their crystal structure has been determined by a single-crystal X-ray structure analysis.

II. RESULTS

Most of human health disorders are treated by a combination of two or more drugs [1]. Up to 25 % of drugs on the market are fixed drug combinations (FDC) which contain physical mixtures of different APIs [2]. As alternative to FDCs, it is possible to assemble different APIs in one crystal lattice by cocrystallization. These new multicomponent drug solids (MCDS) may be salts, cocrystals or their mixtures.

Sildenafil improves penile erections in men with erectile dysfunction [3,4]. Salicylic acid being an important active metabolite of acetylsalicylic acid is also known for its ability to reduce pain and fever [5].

A solid forms of (**sil**)⁺(**sa**)⁻ and (**sil**)⁺(**sa**)⁻(**sa**) were obtained *via* slow solution crystallisation. **Sil** and **sa** were taken in stoichiometric ratio 1:1 for (**sil**)⁺(**sa**)⁻ and 1:2 for (**sil**)⁺(**sa**)⁻(**sa**). Then both dissolved in 3 mL of methanol. Slow evaporation of solvent gave good quality crystals after several days. The **sil** base has been obtained from **sil** citrate monohydrate (*Viagra*[®]) [6].

Compound (**sil**)⁺(**sa**)⁻ crystallizes in the triclinic system, space group $P\bar{1}$ ($Z = 2$) with sildenafil cation and salicylate anion in the asymmetric unit (see Fig. 1a), while (**sil**)⁺(**sa**)⁻(**sa**) crystallizes in the monoclinic system, space group $P2_1/c$ ($Z = 4$) with 2 sildenafil cations, 2 salicylate anions, 2 neutral salicylic acid molecules and 3 water molecules in the asymmetric unit.

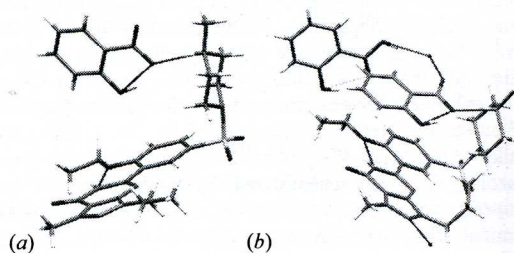
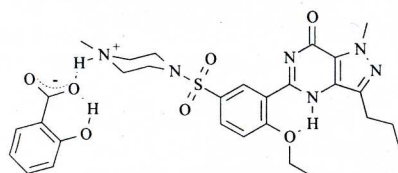


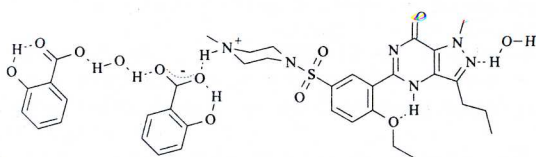
Figure 1. X-ray crystal structure of (**sil**)⁺(**sa**)⁻ (a) and (**sil**)⁺(**sa**)⁻(**sa**) (b) showing hydrogen bonds as green lines

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(a)



(b)

Scheme 1. Chemical structure of (**sil**)⁺(**sa**)⁻ (a) and (**sil**)⁺(**sa**)⁻(**sa**) (b)