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Research Article

A Novel strategies of progesterone: To improving the solid-state of dosage forms by co-crystallization process

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Abstract
Progesterone injection is oily because of its poor solubility. It is necessary to develop new dosage forms or delivery methods for Progesterone with nitrogen heterocyclic compounds (2,6-diaminopyridine, isonicotinamide, 4-aminopyridine, aminopyrazine, picolinamide and pyrazinamide) have been designed and prepared by ethyl acetate-assisted grinding, of which four co-crystals (2,6-diaminopyridine, isonicotinamide, 4-aminopyridine and aminopyrazine) had single crystal in stoichiometry. Metadynamics- generic crossing was used to optimize various Custer structures to explain the reason the other two o-crystals. Shear assisted sono-crystallization is novel techniques for co-crystallization and also used in particle engineering in detailed list out in this article. According to the novel crystal engineering strategies, the co-formers of 2-chloro-4-nitroaniline (CNA), 2,5-dihydroxy benzoic acid (DHB), 4,4"-biphenol (DOD) were prepared by progesterone. The co-crystals were obtained by slow evaporation method and grinding ball mill. These co-crystal were confirmed by X-ray diffraction. IR spectroscopy, powder X-ray diffraction etc, the PROG-CNA co-crystal had the faster rates and highest concentrations as compared to other co-crystal in dissolution experiments. All co-crystals more stable in water and progesterone-pyrazinamide co-crystals featured the best water solubility performance with am approximately. Six- fold increase over free progesterone. This article provides an effective route for designing and manufacturing novel solid states of progesterone.

Keywords: progesterone, pharmaceutical co-crystals, crystal engineering, nitrogen heterocyclic compounds

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1. Introduction

In recent years, novel crystal engineering strategies have been effectively developed to modify the characteristics of a variety of pharmaceutical products. Among pharmaceutical solid-state complexes, co-crystals have attracted increasing attention. Cocrystals are molecular

complexes composed of two or more constituents which are bound in the unit cell through various non-covalent interactions such as hydrogen bonding π-π stacking and vanderwaals interactions the preparation of co-crystals for a given substance offers the advantage of altering the physical and pharmaceutical properties of the drug without modifying its molecular formula specifically, co-crystals with same active pharmaceutical ingredient (API) and different complementary co-crystal formers (CCFs) may show strikingly diverse characteristics, which are directly related to the nature of the CCFF component, such as melting point, solubility. Bioavailability, hygroscopicity, and chemical stability despite the importance of co-crystals, a systematic study of their structure and of the reaction between the structure and the mechanical properties of the co-crystal still remain a rarity. Steroids are play important role in cocrystallization especially in progesterone better than the other steroids like estrogen in life sciences or as pharmacophores.

Progesterone:

Progesterone (PROG) is a naturally and poorly water-soluble steroid drug that belongs to the category of progestins, which are used in birth control pills and menopausal hormone replacement therapies and it is a main bio active progestational hormone secretary by the ovary. PRO cannot only induce the transition of the endometrium to the secretary stage and increase endometrium reacceptance to facilitate the implantation of a fertilized egg but also act on the uterus, providing a good internal environmental for the maintenance of pregnancy PRO injection is oily and advantages of oily injection are the exact curative effect and low scleorma, due to the first pass effect of the liver, the absolute bioavailability of oral PRO is only 6-8%. It is necessary to develop a new dosage forms or delivery methods of PRO.

Table: 1 Introduction of Progesterone

PARAMETERS	DATA
Chemical name	4-prognene-3,20-Dione
Chemical Formula	C21H30O22
Molecular Formula	314.46 g.mol-1
CAS registry No	57-83-0
Melting point	121
Boiling point	447.2
Solubility	Soluble in alcohol Insoluble in water
Stability	Stable in air

Karamertzanis has investigated the···π stacking interaction of different steroids with aromatic molecules and has indicated that the steroid-binding affinity depends on the steroid backbone and especially the A-ring structure. PRO is a good substrate of crystallization because there are two carbonyl groups in the molecule that act as hydrogen bond acceptors, and the steroidal parent nucleus can produce conjugation effects however, the solid-stale complexation of PROG and aromatic molecules has never been systematically studied. In this work, PROG was selected as a co-crystallizing agent, not only due to its attractive backbone but also its terminal carbonyl groups, which provide the possibility for a more abundant network structure. PROG exists in two stable monotropically-related polymorphs: a thermodynamically stable form Ⅰ, with a melting point at 129℃, and a metastable form Ⅱ, with a melting point at 122℃ the co-crystallization of PROG into a suitable co-former may contribute to improving its solid state properties co-crystallizations may be influenced by many factors, including geometry, functional group position, and steric hindrance. Fortunately, the interplay of several interactions in the co-crystal structure provides some guidelines upon which to choose its co-crystals based on crystal engineering principles

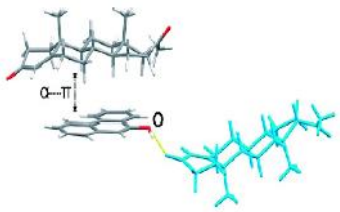

Fig: 1 Crystal structure of a progesterone9-phenanthrol complex

To aim that the further explore the solid-state form of PRO, co-crystals of PRO with 2, 6-diaminopyridine (DMP), isonicotinamide (INA), 4-aminopyridine (AP), aminopyrazine (APZ), picolinamide, (PA) and pyrazinamide (PZA) were prepared and evaluated in stability and solubility. Four cocrystals (DMP, INA, AP, APZ) had single crystal data in 1:1 stoichiometry. Meanwhile, two cocrystals (PA, PZA) had no suitable size for single-crystal X-ray diffraction. This six co-crystal of progesterone were described as stability and solubility of new dosage form of progesterone based upon on meta dynamics- genetic crossing.

The reasons are calculated by MTDGC:

- Metadynamics (Laio and Parrinello, 2002) differs from umbrella sampling in that if introduces memory into the sampling, and it has been described as a method that works by “filling the free energy wells with computational sand”.
- Metadynamics also abbreviated as MTD, METAD OR META D) is a computer stimulation method is computational physics, chemistry and biology.

The calculation results showed that the tetramers (2PRO/2PA) were stable, and the structural fluctuations of the tetramers cluster in ethyl acetate solvent were increased and led to a deficiency in order structure. In contrast to the carboxyl group, the amide group and amino group were good substituents in the pyridine/pyrazine ring. This meant that the cocrystallization of nitrogen heterocyclic compounds containing reactive hydrogen, the

inductive effect played an important role. The co-crystals have been characterized by nuclear magnetic resonance, infrared spectroscopy, thermogravimetric analysis, differential scanning calorimetry, scanning electron microscopy, powder X-ray diffraction and single crystal X-ray diffraction. The stability and solubility have been explored systematically. Although several of PROG cocrystals have been reported in past years, a detailed and reliable structure-activity correlation is still yet to be established between the co-crystal structure and its mechanical properties. As part of an ongoing study in crystal engineering We investigated a series of co-crystals formed by PROG and 2-chloro-4-nitroaniline (CNA), PROG and 2, 5-dihydroxybenzoic acid (DHB) and the PROG and 4, 4-biphenol (DOD) this co-former molecules were chosen based on their ability to interact with the carbonyl group of PROG via the formation of multiple strong hydrogen bonds. Several techniques were used to investigate formation of cocrystals, such as X-ray diffraction, thermal techniques, and spectroscopic techniques. Single crystals of PROG-CNA, PROG-DHB, and PROG-DOD were obtained and characterized by X-ray diffraction to determine their crystal structures

Structure of progesterone:

Biosynthesis of progesterone:

Synthesis of progesterone is a function of the syncytiotrophoblast with maternal cholesterol as its principal substrate; the principal intermediate along the metabolic pathway is delta 5 -pregnenolone, which is converted to progesterone by delta 5 -3-beta-steroid dehydrogenase and delta 5 –isomerase. In mammals, synthesis of progesterone, like all other steroid hormones, is synthesized from pregnenolone which itself is derived from cholesterol. Cholesterol undergoes double oxidation to produce 22R hydroxyl cholesterol, and then 2o α and 22R-dihydroxy cholesterol. The conversion of pregnenolone to progesterone takes place in two steps. First, the ¸3 β- hydroxyl group is oxidized to a Keto group and second, the double bond is moved to C4and C5 through a Keto/enol tautomerization reaction. This reaction is catalyzed by 3βhydroxysteroid dehydrogenase/δ5-4 –Isomerase. Androsternedione to be converted to testosterone, estrone, and estradiol, highlighting the cirtical role progesterone in testosterone synthesis. Pregnenolone and progesterone can also be synthesized by yeast. Approximately 25mg of progesterone is secreted from the ovaries per day in women, while the adrenal glands produce about 2mg of progesterone per day.

Chemistry of progesterone:

Progesterone is a naturally occurring pregnane steroid and also known as pregn-4-ene-3,20-Dione it has a double bond between C4 and C5 positions and two ketone groups, one at 3-position, and other at C20 position. Progesterone is commercially produced by semisynthesis. Two main routes are used: one from yam diosgenin first pioneered by marker in 1940, and one based on soy phytosterols scaled up in the 1970s.

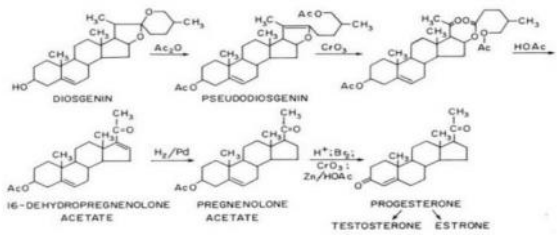

Fig: 2 Diosgenin

Various dosage form in progesterone:

Progesterone is a hormone that is naturally produced by the body and is used in various forms to treat a range of conditions:

- Progesterone are available in various forms like oral tablets and capsules ,vaginal gels ,injections , suppositories
- The dosage and duration of treatment depend on the medical condition being treated and the patients response to the medication
- For example: Oral capsules are used to prevent thickening of the lining of the uterus [Endometrial hyperplasia] and for the treatment of unusual stopping of menstrual periods [Amenorrhea]
- Vaginal gels are used to treat infertility in women who don't ovulate regularly
- Injections are used to prevent preterm birth in women who have had a previous preterm birth
- Suppositories are used to treat secondary amenorrhea

2. Medical uses of progesterone

Progesterone is hormone that has several uses in women like

- Thickening the lining of uterus for implantation
- Regulating bleeding during menstruation
- Supporting a pregnancy once conception occurs
- Helping to improve your mood
- Supporting thyroid function

Progesterone uses in pregnancy:

- The fertilized egg be implanted in the uterus to establish a pregnancy for the
- Maintain a healthy pregnancy
- "prep" the uterus fertilized embryo

Treatment for progesterone:

Progesterone treatment can be administered in several ways like

- Creams and gels which can be topically or vaginally
- Suppositories ,which are commonly used for treat low progesterone that causes fertility problems
- Oral medications ,like plover

Co-crystallization of progesterone:

Co-crystallization: It is a process of forming crystals

Co- crystal: Cocrystals are crystalline solids that contain two or more different molecules in the same crystal lattice. They are used to improve the physical and chemical properties of drugs such as solubility, stability, and bioavailability.

Cocrystal of progesterone:

The cocrystal is formed by the active ingredient progesterone and a cocrystal former which is selected from isophthalic acid, 4-formylbenzene boronicacid ,and 3-nitrophthalic acid the patent also describes the method for preparing the cocrystal of progesterone and its use for increasing the thickness of endometrium improving progesterone's solubility , or increasing progesterone's permeation rate. A novel technique has been developed for producing progesterone form 2 crystals by shear – assisted sonocrystallization method progesterone, a steroid hormone ,has been recognized for more than 70 years as having two polymorphs, a stable form (form1) and a metastable (form2) previous attempts have failed to produce a single crystal of form2 of progesterone without the presence of a cocrystal additive or template this technique proposed in the current study is the first to report the growth of single crystals of progesterone form 2 the produced crystals were characterized using X-ray diffraction, differential scanning calorimeter, and fourier transform infrared spectroscopy. single crystal X-ray diffraction was performed for comparing the hydrogen bond geometry of form 1 and 2 .

The SAS technique can be proposed as a novel strategy for polymorphic transformation of progesterone, which can increase the dissolution rate, enhance oral bioavailability, and decrease dose-related side effects.

Shear –assisted sonocrystallization:

- It is a technique that combines the benefits of both ultrasound and shear to control the nucleation and crystal growth of a crystallization process
- This technique has been found to be effective in producing smaller particle sizes with narrower size distribution , decreased induction time ,metastable zone ,super saturation levels or a stability increase
- This technique is particularly useful in the production of active pharmaceutical ingredient

The solid form crystallization, and particle engineering are core elements linking the final step of the synthesis pathway of API manufacture to the drug product attributes crystallization is the final step of API manufacture that must be controlled and reproducible providing API of suitable quality in terms of both purity and appropriate physical properties for dosage form design robust product processing

Preparation of Co-Crystals:

The co-crystals were prepared using a slow evaporation technique and also ethyl acetate assisted grinding in a ball mill. The same procedure was used for each co-crystal experiment; the only difference was in the volume of solvent and amounts of starting materials used. The general procedure involved dissolving equimolar amounts of PROG and the selected co-former in a suitable solvent and subsequently stirring at room temperature. After all compounds had been dissolved in solvent, the resulting solutions were filtered into vials and left for several days after each vial had been covered with Parafilm™. Various single crystals of the co crystals were filtered for further screening.

3. Crystal structure of analysis

As observed in the three co-crystals, four typical hetero-pythons (Scheme 2) were formed due to the strong hydrogen bonding network which involves the amino group, the carboxylic acid, and the As observed in the three co-crystals, four typical hetero-synthons (Scheme 2) were formed due to the strong hydrogen bonding network which involves the amino group, the carboxylic acid, and the hydroxyl group as donors and the carbonyl group (cycloketo and acetyl) as acceptors. These hydrogen bonding interactions strengthen the stability of the three co-crystals. hydroxyl group as donors and the carbonyl group (cycloketo and acetyl) as acceptors. These hydrogen bonding interactions strengthen the stability.

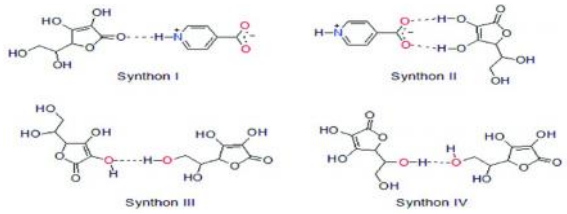

Fig: 3 chemical structure of analysis

Nitrogen heterocyclic ring CCFs that cannot form cocrystals with PRO:

Under ethyl acetate-assisted grinding conditions, some nitrogen heterocyclic ring CCFs could not form cocrystals with PRO, such as heterocyclic amino acid and purine/ pyrimidine. There were probably two reasons. One was the hydrogen bound to the CCF too tightly: the other was the CCFs themselves being prone to forming intermolecular / intermolecular hydrogen bonds. As a result, they failed to form cocrystals with PRO.

Stability analysis:

Stability experiment was performed to investigate the physical stability and transformation of the sample under different storage environments and physiological conditions. PRO and six cocrystals all showed excellent physical stability in high temperatures, high humidity, high light intensity condition and in water suspension conditions.

Dissolution rate of progesterone:

Solubility was closely related to the bioavailability of the drugs in vivo. Since PRO has poor solubility in water (0,41

mg.ml-1), the synthesis of cocrystal is attractive. PRO-DMP / INA/ AP/APZ/PA featured1.22 mg.ml-1 , 1.74 mg.ml-1 . 1.81 mg.ml-1, 1.55 mg.ml-1 and 1.63 mg.ml-1 respectively, being 3-to 4,5 fold equilibrium concentration in water when compared with PRO used in the solubility experiments. In particular, for PRO-PZA, the equilibrium concentration reached 2.65 mg .ml-1 , which has 6-5 fold as large as the solubility of free PRO. This result suggested that PRO-PZA could be a suitable candidate for novel PRO pharmaceutical formulations with improved solubility.

General analysis:

The PXRD patterns of six cocrystals showed that the diffraction peaks had obvious differences in the position, number, strength, geometric topology and so on SEM images showed that each cocrystal had unique crystal habits and morphological characteristics. PRO had block morphology, PRO-DMP, and PRO-PA had smaller flake morphology, PRO-INA had bigger flake morphology, PRO-APZ, PRO-AP, PRO-PZA had irregular morphology.

According to the FT-IR spectra, the asymmetric starching vibrations at 3500-3100 cm-1 indicated the presence of the amino or amide groups in all six cocrystals. The chemical shift of PRO in ^{1}H-NMR was CCFs in all six cocrystals range between 0.67 and 5.63ppm, and nitrogen heterocyclic compounds had a higher chemical shift between 5.63 and 9.18ppm. The melting point of PRO and six cocrystals.

Table:2 melting point of co-crystals of progesterone

Compounds	Melting point (°C)
PRO	132
PRO-DMP	110
PRO-INA	130
PRO-APZ	112
PRO-AP AND PRO-PA	122
PRO- PZA	126

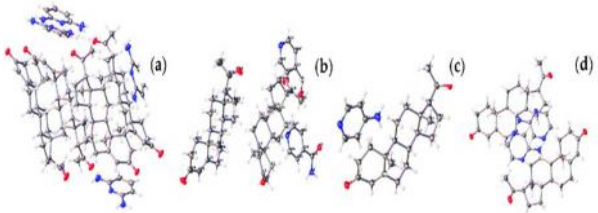

Fig:4 Structure of (a) PRO-DMP, (b) PRO-INA, (c) PRO-AP, and (d) PRO-APZ

Structure of the prog-cna co- crystal:

The single crystals of PROG-CNA were obtained by the evaporation method. And it is co-crystal belongs to the orthorhombic system. The CNA molecule contains a nitro group as a hydrogen–bonding acceptor and an amino group as hydrogen-bonding donor. Hence this CNA into a sort of "traffic hub" holds together the interaction network from the different parts of the different parts of co-crystal. Head-to-tail adjacent PROG molecules are linked to a CNA molecules via synthons 1 and 2 as shown in fig:4. This is called a zig-zig chain. In a PRO-CNA, N atom undergoes sp3 hybridization with an angle is 108.5. The conjugation between nitro group and its benzene ring then may caused formation of the C-H…O hydrogen bond between the CNA homo-molecules and CNA hetero-atom of CNA and PROG. Hence this chemically changes enhances the solubility of the 3D structure of the co-crystal in their solid structure. In ring motif, multiple C-H..O|N hydrogen bonding (as shown in fig:4) between PROG and neighboring CNA molecules enhance the stability of 3D structure of co-crystal.

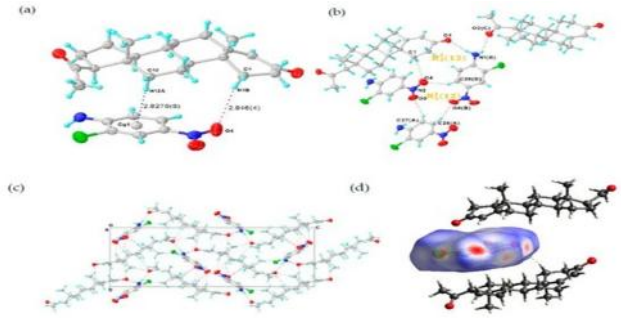

Fig: 5 PROG-CNA co-crystal

Structure of the PROG-DHB CO-CRYSTAL:

DHB having a dual nature between the hydrogen-bonding donor and hydrogen-bonding acceptor in the co-crystals and also exist the more efficient "traffic hub" than CNA. Stillinovic and co-workers have investigated the proton transfer of salts | co-crystal between DHB and its pyridine derivatives. And also Leo and co-workers was investigated study of positional isomerism of the hydroxyl groups in a DHB molecule co-crystallization with piracetam. DHB makes a more effective CCFs in many co-crystals because one extra hydroxyl group. DHB plays a significant role for PKa value of the solid formation between the DHB and CCF. DHB and PROG are combine with the synthons 3 as shown in, and also ring motif to form a hetero-molecule dimer (fig:3). The strong hydrogen-bonding interaction between the hydroxyl group and acetyl carbonyl group of PROG. Carbonyl group undergoes conjugation the remaining hydroxyl group form a intermolecular hydrogen bond.DHB acts as a hydrogen bond acceptor and it connects to the adjacent PROG molecular layer. Hence it is stabilize the solid structure of the co-crystal.

Structure of the prog-dod co-crystal:

PROG-DOD is a monoclinic crystal system and a longer backbone of the DOD molecule compared that the PROG-DHB, PROG-CNA. DOD has 2 hydroxyl groups are positioned at both ends of the DOD molecule. Linearly-shaped molecular structure generates an extremely different interaction with PROG. DOD acts as "canal " that links the PROG located at both ends of the structure rather than " traffic hub " that holds the complicated network. PROG-DOD has a unit volume that indicates the three molecular pairs are arranged in asymmetric unit as that the DHB and CNA. The three DOD molecules having a intramolecular benzene as compared to DHB and CNA.

Each single DOD molecule shows a different symmetry and the co-crystal structure belongs to a low symmetry space group. The PROG and DOD molecule form the hetero-molecule dimer via synthon4.This network generate a triangle-like motif. The 3D structure of PROG-DOD molecule is generated by stacked ladders linked together via multiple C-H..O interactions. Weyna and co-workers had reported that the DOD molecule co-crystallizes with linear bipyridyl compounds and adopts a zipper-type structure due to linear co-crystal unit.

Techinques Used for the Co-Crystals of Progesterone:

The co-crystals show a characteristics special pattern which is similar to the ones of PROG and CCFs. The frequencies of the C═ O stretching vibrations in the co crystals appear blue-shifted due to formation of the C═O interaction between the PROG molecule and the CCFs. The IR spectrum of PROG-CNA shows the two carbonyl vibrations appear at 1627.91 cm-1 and 1585.48 cm-1, PROG-DHB appear at 1674.20 cm-1 and 1612.49 cm-1 and PROG-DOD appear at 1612.49 cm-1. The stretching vibrations the C-H bonds of PROG in the co-crystals appear the red shift while the peaks as appear at 3371cm-1, 3209cm-1and 3440cm-1 in PROG-CNA, PROG-DHB, PROG-DOD. All these frequencies are clearly higher than 2943cm-1within the C-H of the PROG molecule. This effect may be explained by the presence of a weak C-H..O or C-H π interaction which induces the formation of more stable structures.

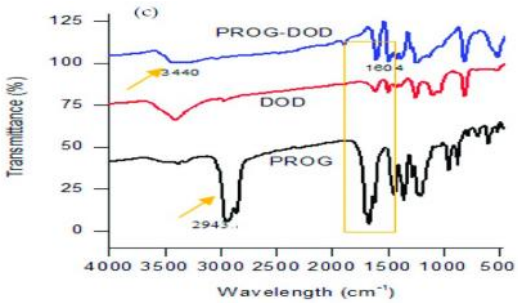

Fig: 6 Combined FT-IR spectra of DOD, PROG-DOD, and PROG

4. Conclusion

Progesterone is most important for cocrystallization than estrogen. Co-crystallization of progesterone are prepared by slow evaporation method, ethylene assisted under grinding ball mill and shear assisted sono-crystallization was found to be co-crystals of progesterone like 2-chloro-4-nitroaniline(CNA), 2,5-dihydroxy benzoic acid(DHB), 4,4”-biphenol (DOD) by using slow evaporation method and six co-crystals by using grinding ball mill. Six co-crystals of progesterone were determined the stability and solubility of drug, of which four co-crystals had single crystals data. They were more soluble than PRO. Based on novel crystal engineering strategies, PROG-CNA, PROG-DHB, PROG-DOD was stability and solubility of drug. DHB and CNA have more stability than DOD due to the complex hydrogen bonding pattern in the co-crystal structure and multiple weak interaction. The linear shape of the DOD molecule generates a broader connectivity pattern in the co-crystal structure. all co-crystals structures were confirmed by powder X-ray diffraction spectroscopy, IR spectroscopy. The dissolution tests indicate that faster rates and higher concentrations of PROG were attained after co-crystallization. CNA and PROG, more stable and abundant interactions which are composed of multiple C-H..N hydrogen bonding and α-π interactions finally, the investigated of crystal structure provides positive support for the selection of suitable co-former using the crystal engineering strategies.

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