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Research Article

Development of Co-Crystallization Technique to Improve Solubility of Anti-Diabetic Drug

Ninad S. Burkhande[1*], V. P. Wankhade[2], S. C. Atram[3], N. N. Bobade[4], S. D. Pande[5]

[1] Student M- pharmacy, Department of Pharmaceutics, Vidyabharati College of Pharmacy, Amravati, Maharashtra,India-444602

[2] Guide,Vidyabharati College of Pharmacy, Amravati, Maharashtra,India–444602.

[3] Associate Professor,Vidyabharati College of Pharmacy, Amravati., Maharashtra,India–444602.

[4] Associate Professor,Vidyabharati College of Pharmacy, Amravati., Maharashtra,India–444602.

[5] Principal, Vidyabharati College of Pharmacy,Amravati, Maharashtra,India–444602.

ABSTRACT

Co-crystallization is a useful crystal engineering approach for changing the physiochemical and structural characteristics of drug crystals. Pharmaceutical co-crystals are nonionic supramolecular complexes that can be utilized in pharmaceutical development to change physiochemical qualities including solubility, stability, and bioavailability without changing the chemical makeup of API. Canagliflozin Hemihydrate is a anti-diabetic drug. Canagliflozin belongs to class IV drug in BCS classification. i.e. low solubility and low permeability. The major problem of this class drug is it slow solubility in biological fluids,which results into poor bioavailability after oral administration. The purpose of this study was to prepare pharmaceutical co-crystals ofCanagliflozin to enhance solubility and dissolution rate by using co-crystallization technique. The co-former used inthis study is Thiourea. The Optimized co-crystal was characterized by FTIR, XRPD, SEM and other pharmaceutical properties like solubility and melting point were alsoevaluated.

Keywords: Co-crystals,Canagliflozin,Co-crystallization,Solubility

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*Address for Correspondence:
Ninad S. Burkhande, Department of Pharmaceutics, Vidhyabharti College of Pharmacy, Amravati, Maharashtra, India-

INTRODUCTION:

Canagliflozin hemihydrate is in anti-diabetic class of drug. The mechanism of Canagliflozin is of the gliflozin class or subtype 2 sodium-glucose transport (SGLT-2) inhibitors class.The sodium-glucose co-transporter2 (SGLT2), is found in the proximal tubules of the kidney, and reabsorbs filtered glucose from the renal tubular lumen. Canagliflozin inhibits the SGLT2 co-transporter. This inhibition leads to lower reabsorption of filtered glucose into the body and decreases the renal threshold for glucose (RTG), leading to increased glucose excretion in the urine.Canagliflozin belongs to class IV drug in BCS classification i.e. low solubility and low permeability. The major problem with this class drug is its low solubility in biological fluids, whichresults into poor bioavailability after oral administration. Co-crystallization is an efficient crystal engineering approachfor modifying the crystal structure and properties of drugs. Co-crystallization can improve physiochemical propertieslike solubility, dissolution rate, chemical stability and melting point without affecting chemical composition of API.

Co-crystallization is a recent crystallization method that allows binding two or more building blocks within one periodic crystalline lattice without making or breaking covalent bonds. These building blocks are neutral molecularspecies coupled via hydrogen bonds. Multi-component crystals e.g. solvates, hydrates, co-crystals, salts play vital rolewithin the design of recent solids significantly in the pharmaceutical industry. Pharmaceutical co-crystals are nonionic supramolecular complexes and might be wont

to altered property problems like solubility, stability and bioavailability in pharmaceutical development while not affecting chemical composition of API. Co-crystals are often outlined as crystalline complexes of two or additional neutral molecular constituents sure along within the lattice through non covalent interactions (primarily hydrogen bonding). The formation of pharmaceutical co-crystals involves in corporation of a given API with another pharmaceutically acceptable molecule (Co-former) within the lattice. Co-crystal comprising of API and desired ratio acceptable co-crystal that may be created by varied forms of interaction like hydrogen bonding, π-stacking and Vander wall forces. The ensuing multi-component crystalline part can maintain the intrinsic activity of the parent API. [1-9]

Materials and Methods:

Canagliflozin Hemihydrate was received as a gift sample from Morepen Pvt. Ltd. Solan (Himachal Pradesh).Thiourea used as co-former. All other materials were used of laboratory grade.

Preparation of Co-Crystals:

Sono-Crystallization Methods[10]:

The sono-chemical methodology was developed for preparation of organicco-crystals in very finitesize. During this technique, the pure drug Canagliflozin and co-formers (Thiourea) invarious ratios (1:1), (1:2), (1:3), (1:4), (1:5) are dissolvedin a common organic solvent (Methanol) and kept for sonication in bath sonicator at a constant temperature. Cold wateris provided so as to keep up a constant temperature of bath sonicator. The air bubbles or voids are created because ofthe high energy, that produces size reduction and supersaturation, causes crystallization. During this stage the solution of molecules are expected undergo various hydrogen bonding reactions. Then mixture poured in Petridish and kept it in room temperature till all the organic solvent got evaporated. The formation co-crystals are done by further evaporation of the solvent acceleration.

Screening of co-formers:

The screening of co-formers was performed by comparing the solubility of pure drug with co-crystals of pure drug &co-formers (Thiourea) in different concentration ratios (1:1), (1:2), (1:3), (1:4), (1:5). Form each preparation, anequivalent amount of 10 mg of drug was added to each media in glass vials with caps. The vials were kept in Shakermaintained at 37 ±0.5°C for few hours, after that the solution was centrifuged and filtered. The filtrate was suitablydiluted with distilled water and analyzed using a double beam UV spectrophotometer (UV1800; Shimadzu, Kyoto, Japan) at λ_{max} of pure drug.

Characterization of optimized co-crystals:

1. Solubility Study of pure Canagliflozin and Canagliflozin optimized co-crystals[11]

The solubility of pure Canagliflozin and Canagliflozin-Thiourea Co-crystals was determined in various non-volatile solventsby adding an excess amount of drug to 10 ml of selected non-volatile solvents (Distilled water, 0.1N HCl, pH 6.8phosphate buffers) in stoppered vials. The vials were kept at 25± 0.5°C in shaker for few hours to reach equilibrium.The equilibrated samples were removed from the shaker and kept in centrifuge machine for centrifugation for fewminutes. After that the supernatant was taken and filtered through filter paper and concentration of Canagliflozin wasdetermined in the non-volatile solvents after dilution was check using UV-Visible spectrophotometer at selected λ_{max}wave length.

2. Melting Point [12]

The melting point determination is done by capillary tube method. This method involves filling of a small amount of Canagliflozin-Thiourea co-crystals in a one side sealed capillary tube and joining this to athermometer. Then capillarytube is placed into a Thiele's Tube which is filled with paraffin oil and heat the Thiele's tube on Bunsen Burner. Thesetup of apparatus is manual with the aim of heating up a Canagliflozin-Thiourea co-crystals sample inside a capillary tubewhilst visually looking for when the Canagliflozin-Thiourea co-crystals sample has melted. This melted temperature isnoted as melting point of Canagliflozin-Thiourea co-crystals. It is important to heat the sample slowly using this method sothata thermal equilibriumcanbe established.

3. Fourier Transform Infrared Spectroscopy analysis of pure Canagliflozin and Canagliflozin optimized co-crystals [12]

Fourier Transform Infrared (FT-IR) spectroscopic analysis of pure Canagliflozin and Canagliflozin-Thiourea Co-crystals was carried out to assess its purity. The Infrared spectrum of pure Canagliflozin and Canagliflozin-Thiourea Co-crystals was taken on FTIR spectrophotometer (SHIMADZUJAPAN).Weight accurately few mg of dry IR Grade KBr and grindinmortar pestle. Add about 2-3 mg of sample and grind with KBr in the mortar until there was no evidence of crystallinity and uniformd is tribution throughout the KBr. The sample was an alyzed in the range of 400cm-^{1}to4000cm-1.Theobtained FTIR spectrum was studied and compared with standard reference and interpreted. In addition, the size of the peaks in the Spectrum was a direct indication of the amount of material present.

4. Crystallographic methods (XRDs) analysis of optimized co-crystals[13]

X-ray diffraction (XRD) was a strong non-destructive technique for characterizing crystalline materials. The atomicplanes of a crystal cause an incident beam of X-rays to interfere with each other as they leave the crystal. Thephenomenon is termed X-ray diffraction. It provides data concerning structures, phases, preferred crystal orientations (texture),and different structural parameters, like average grainsize, crystallinity, strain, and crystal defects.

This technique has two basic steps. In 1st step, the Canagliflozin-thiourea co-crystal sample was placed in an intense beamof X-rays (single wavelength monochromatic X-rays) which produces the regular pattern of reflections.

The angles andintensities of diffracted X-rays are measured because each compound having a unique diffraction pattern. As the crystalgradually rotated, previous reflections disappear and new ones appear. The intensity of every spot was recorded atevery orientation of the crystal. The sets of multiple data may had collected, each set covering slightly more than half afullrotation of the crystal and typically containing tenthous and of reflections.

In the second step, this information was combined computationally with complementary chemical data to produce and refinea model of the arrangement of atoms inside the crystal. The final, refined model of the atomic arrangement now called a crystal structure was usually stored in a public database. X-ray diffraction peaks are produced by constructiveinterference of amonochromatic beam of X-rays scattered at specific angles from every set of lattice planes in asample. The peak intensities were determined by the distribution of atoms within the lattice. Consequently, the X-ray diffraction pattern was the fingerprint of periodic atomic arrangements in a given material.

5. Scanning Electron Microscopy (SEM) of optimized co-crystals[14]

Scanning electron microscopy (SEM) was conducted to characterize the surface morphology of the particles withexcellent ease and efficiency. SEM differs from other electron microscope wherein the image was duly obtained rightfrom the electrons that are strategically emitted by surface of an object in comparison to the transmitted electrons.Electron microscopy techniques, like scanning electron microscopy (SEM) can be utilized for particle sizing, and theygive at the same time also particle shape and morphology information. Scanning electron microscopy requires highvacuum, and clean, dry and electrically conductive samples. This often means that samples needs to be for example platinum or gold coated before the measurement, which can alter the surface characteristics. If sample needs to be driedbefore analysis, drying method can alter also the sample properties. More advanced technique was environmentalscanning electron microscopy, ESEM, which does not require high vacuum, and wet or oily samples can be analyzed. Scanning electron microscopy techniques was recommended for particle shape analysis.

RESULTSANDDISCUSSION:

Screening of Co-formers:

Table 1: Screening of co-formers

Sr. No.	Ratio of Drug and Co-former	Observed Solubility of Canagliflozin using Thiourea
1	1:1	0.073
2	1:2	0.02421
3	1:3	0.04181
4	1:4	0.03667
5	1:5	0.04392

The screening data in distilled water with screening of co-formers was found that the solubility of canagliflozin with thiourea in 1:1 ratio is highest in distilled water.

Characterization of optimized Canagliflozin-Thiourea Co-crystal:

1. **Solubility study of canagliflozin and canagliflozin-thiourea co-crystals**

Table 2: Solubility study of Canagliflozin

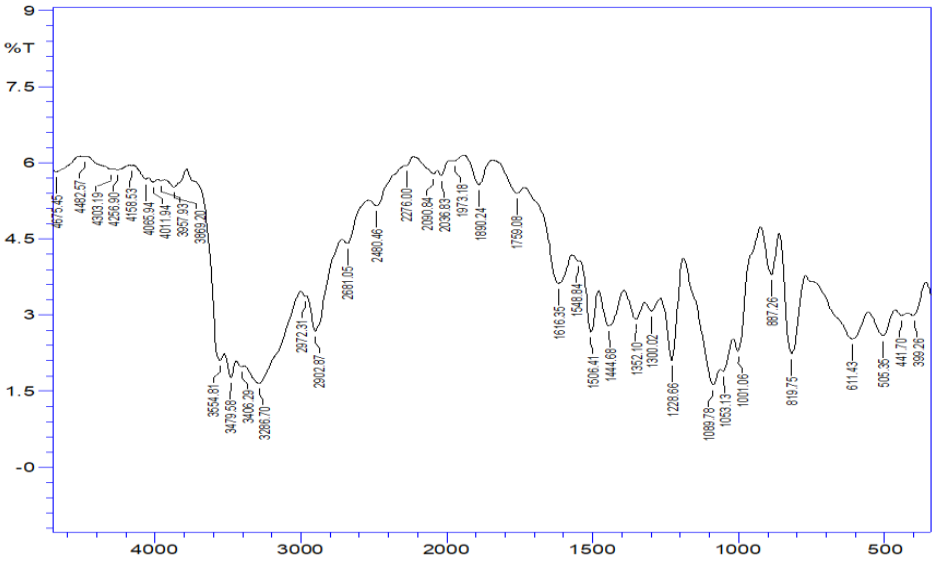
Sr. No.	Name of Solvent	Solubility mg/ml
1	Distilled water	0.00112
2	0.1N HCl	0.00138
3	Phosphate Buffer pH 6.8	0.0687
4	Ethanol	5.5

Table 3: Solubility of canagliflozin-Thiourea co-crystal:

Sr. No.	Name of solvent	Solubility (mg/ml)
1	Distilled water	0.053
2	0.1N HCL	0.013
3	Phosphate Buffer pH 6.8	1.309

2. **Melting Point:** The melting point of Canagliflozin-Thiourea Co-crystal was determined by capillary tube method. It was found to be 100^0C.

3. FTIR of Canagliflozin:



Sample Name- Canagliflozin Hemihydrate **1/cm**

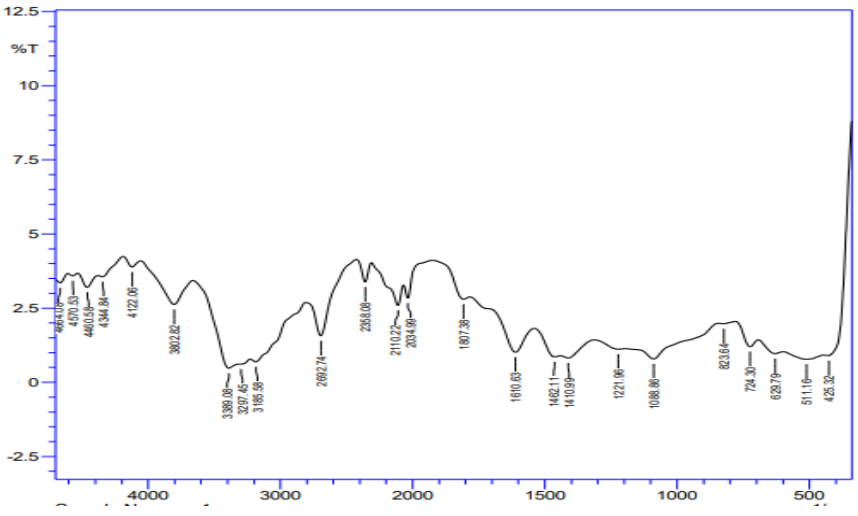
Figure 1: FTIR of Canagliflozin

The FTIR spectrum of pure Canagliflozin was taken and the peaks values of different functional groups after interpretation were shown in table.

Table 4: Interpretation of FTIR spectrum of Canagliflozin

Sr. No.	Functional Group	Observed Peaks $(cm)^{-1}$
1	Free -OH group (OH Stretch)	3479.58
2	C-H Stretch, Aromatic	3286.70
3	C=C ring Stretch, Aromatic	1444.68
4	C-H Stretch, CH_3	2902.87
5	CF Stretch, Aryl Fluorides	1228.66

FTIR of Canagliflozin-Thiourea co-crystal:



Sample name: Canagliflozin-Thiourea Cocrystal **1/cm**

Figure 2: FTIR of Canagliflozin-Thiourea Co-crystal

Table 5: Interpretation of FTIR spectrum of Canagliflozin

Sr. No.	Functional Group	Observed Peaks $(cm)^{-1}$
1	Free -OH group (OH Stretch)	3389.08
2	C-H Stretch, Aromatic	3185
3	C=C ring stretch, Aromatic	1462.11
4	CH Stretch, CH_3	2692.74
5	CF Stretch, Aryl fluorides	1221.96
6	-NH Stretching	2289.08
7	1^0 Amines C-N Stretching	1088.86
8	C=S stretching	629.79

4. Crystallographic methods (XRDs) analysis of optimized co-crystals:

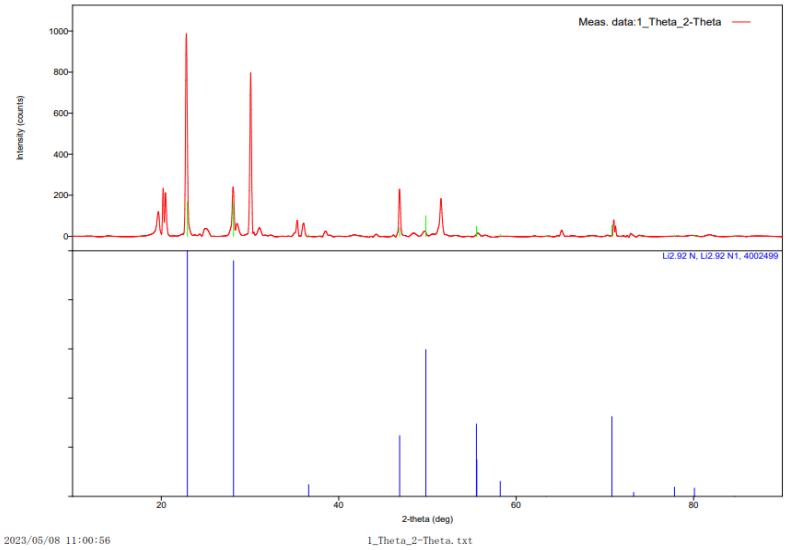


Figure 3: XRD of Canagliflozin-Thiourea Co-crystals

The Canagliflozin- Thiourea Co-crystals exhibit the 2-theta (deg) range 22.94 – 98.30 and shows intense crystalline peak. Diffraction peaks of Canagliflozin-Thiourea Co-crystals were observed at 2-theta (deg) values indicating the crystalline nature of Canagliflozin-Thiourea Co-crystals.

5. Scanning Electron Microscopy :

Scanning electron microscopy of formulation showed needle shape structure less crystals showing entrapment of drug and size found to be 1µm.

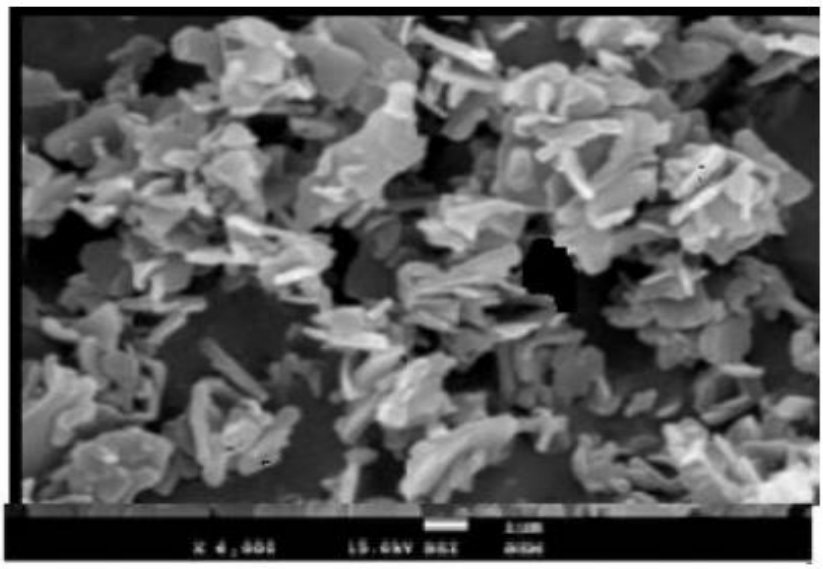


Figure 4: SEM of Co-crystals

CONCLUSION:

The aim of this study was Co-crystallization as solubility enhancement technique for development of tablet using poorly soluble drug form i.e. (Canagliflozin Hemihydrate). The result obtained from executed experiment it can be conclude that, the drug, Co-former and excipients were evaluated for confirmation. Co-crystals of Canagliflozin was prepared by Sono-crystallization Method using various compounds as co-former with different ratios. By using thiourea as a co-crystal former give maximum solubility and dissolution rate. From the above discussion it is clear that improvement in solubility and dissolution rate of Canagliflozin can be achieved by co-crystals. In vitro dissolution of optimized Canagliflozin-Thiourea Co-crystals tablet was comparatively higher than Pure Canagliflozin API tablet formulation which reflects improvement in solubility. From the study carried out it was concluded that stable Canagliflozin-Thiourea Co-crystals and tablets of optimized Canagliflozin-Thiourea Co-crystals with increased solubility and improved in vitro dissolution can be successfully prepared.

Co-crystals was prepared in the present study can further goes for animal studies. Co-crystals can be form by using various methods other than the Sono-crystallization Method which is used in the present study. The co-crystals of poorly soluble drugs can be used as an active pharmaceutical ingredient (API) in dosage form.

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