Phase Transitions Among of Valsartan Polymorphs
Due to Grinding and Humidity Variantios

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Abstract
Phase transition between drugs with polymorphisms needs attention due to unconscious changes in quality. Valsartan (VAL) is a drug model with polymorphic events to be studied here. All phase forms originate from recrystallization through various organic solvents such as acetonitrile and n-butyl acetate. So as a comparison, this study used starting materials (from the market) that were not treated. The grinding and humidity variations (RH 75% and 98%) treatment were studied in a phase transition. The polymorphic changes characterization was observed by microscope light polarization (PLM), Fourier Transform Infrared (FTIR), and Powdered X-ray Diffractometer (PXRD). Polymorphic transformations between VAL treatments were observed using PXRD. There were significant differences in morphology, IR spectra, and diffractograms pattern. Found that the untreated VAL was amorphous, whereas the others were in high crystallinity. The resulting phase of n-butyl acetate shows the behavior of a metastable phase that tends to change to a stable crystal (like the product phase of acetonitrile).

Keywords: Valsartan, Phase transition, Polymorphism, Recrystallization

1. Introduction
The ability to find the polymorphism of pharmaceuticals during manufacturing processes is critically important. Since known the pharmaceuticals compound exhibits poly-morphism, that means changing different physicochemical properties at the site made the industry more cautious. Crystallization conversion during unit operations like milling and granulation is commonly hidden [4,6]. The pharmaceutical industry is necessary to ensure that only the polymorph specified in the regulatory fulfill is immanent in the formulation so that they must keep the quality of the product not turn to unacceptance criterion [3].

Valsartan (VAL), N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl) [1,1'-bi-phenyl]-4-yl]-methyl]-L-valine, as selective angiotensin II type 1 receptor blocker choose widely for the treatment of
hypertension [7]. This pharmaceutical compound reported having 12 different polymorphs and amorphous form [1]. Unfortunately, there is a lack of information regarding the changes in the properties of these polymorphs, especially about transition during the manufacturing.

The habit or morphology of crystals generally is obtained from solution saturation, stirring rate, cooling rate, solvent mixture, additives, crystal seeds, temperature, and impurities. Among the various methods, the variation of the dielectric constant of the solvent is effective and practical in obtaining some phase [8]. Caused by finding different polymorphic forms in pharmaceuticals solid among commercial products will take much more time, unrealistic, and inefficient. Therefore, this study aims to learn polymorphic changes under mechanical forces like grinding and humidity variation environments among phases of VAL. Meanwhile, all VAL phases were produced by recrystallizing the selected solvents. The information resulting useful for pharmaceutical development if there want to be applied vary of polymorph forms.

![Structure formula of Valsartan](image)

Fig. 1. Structure formula of Valsartan [7].

2. MATERIALS AND METHODS

Materials

Valsartan (VAL) was obtained from Zhejiang Huahai Pharmaceutical Co., LTD. (Batch No. CS271-13-196). All other chemicals used were of analytical grade. The solvents used n-butyl acetate and acetonitrile was applied without any purification.

3. Methods

2.1 Polymorphs preparation

The VAL bulk powder from the market was amorphous form. To earn different crystal forms of VAL was obtained with recrystallization by two organic solvents. An amount of VAL was dissolved in some volumes of solvent (n-butyl acetate or acetonitrile) at 15 – 20°C for an hour. Then the solutions (or suspensions) dried at room temperature. After several hours the solid phase appears, collected in a separate container, and labeled.

2.2 Polarization Light Microscope

The morphology of crystalline habit may observe firstly by Olympus BX53 model U-LH100-3 microscope with 400 x magnification.

2.3 Fourier Transform Infrared (FTIR) Spectroscopy

The sample fingerprints functional groups were recorded by IR Prestige-21 Shimadzu, Japan. The samples were dispersed in KBr powder and compress by a hydraulic press to form a compact transparent disc. The spectrum of each sample was recorded from 400–4000 cm\(^{-1}\).

2.4 Powder X-ray Diffraction (PXRD)

Powder X-ray diffraction (PXRD) was conducted by X-ray diffractometer (X’Pert-Pro PANalytical, Netherland) with Cu–K\(\alpha\) radiation (1.5 Å), at 40kV, 30 mA, and fixed divergence slit 0.05o, receiving slit 0.45 mm. All samples were scanned at room temperature in the 20 range of 5–50o with 0.02 step size and 0.8 s per step, care was taken to avoid phase transitions during preparation.

2.5 Polymorphic Transformation Evaluation
Mechanical Forces Influence (Grinding)
Considerable amounts of VAL polymorphs were ground in Retsch RM 200 at 100 rpm for 30, 60, and 90 minutes. The phase transition among polymorphs was monitored with an X-ray diffractogram.

Humidity Influence
Stored some VAL polymorphs under humidity-controlled on desiccator at room temperature with RH 75% (NaCl supersaturation) and 98% (K2SO4 supersaturation) for a month, and take samples every a week to observed by PXRD.

4. RESULT AND DISCUSSION

Polarization Light Microscope
The recrystallization produced among polymorphs was monitored through different habit morphology with a polarization light microscope. From microscopic images found the habits modification resulted, as seen in Fig. 2. As shown in the figure, the crystal habit of a 400 x magnification polymorph of acetonitrile in smaller rods than the crystals of n-butyl acetate.

Fourier Transform Infrared (FTIR) Spectroscopy
The spectrum showed a similar pattern of functional group fingerprints, which proved those powders are the same substance. It looks a little different at 3456 cm⁻¹ bands as represent of O–H stretch, there found in untreated VAL has a broad O–H stretches that indicate as amorphous has a more hydrophilic group. Other bands such as those at 2962 and 2360 cm⁻¹ representing the C–H and C=O bands appear to shift slightly in different polymorphs. The fingerprint pattern around 500–2000 cm⁻¹ shows very little shift but is still in the same spectrums pattern. This variation among polymorphs indicates that the solvent has interaction to affect crystaline modification among VAL.

3.1 Powder X-ray Diffraction (PXRD)
Lastly, the powerful distinguishing among crystals using powdered X-ray diffractionogram. As shown in Fig. 4 those powders have a very disparity ordered arrangement. The starting materials of VAL has shown an amorphous form which has to shorten ordered
than another polymorphic form resulted from solvent recrystallization. Those looks that polymorph came from acetonitrile more crystalline than n-butyl acetate. The crystal from acetonitrile has 20 peaks at 10.7°, 13.8°, 18.5°, 20.0°, and 20.5°, while from n–butyl acetate has 20 peaks at 5.2°, 9.5°, 10.4°, 11.6°, 12.7°, 13.8°, and 14.2°.

3.2 Polymorphic Transformation Evaluation

The resulting polymorphs are then treated in the form of energy variations such as mechanics through milling and various humidity environments in storage, which can cause changes in product quality in the manufacturing process. The phase change between the VAL forms was observed, the acetonitrile product phase changed to an amorphous form after 90 minutes of milling, while the VAL form was produced from n-butyl acetate at 30 minutes of milling had a diffractogram pattern to the polymorphic form of acetonitrile. Under humidity, the VAL from acetonitrile is shown unchanged even at RH 98% after a month stored, but the VAL from n-butyl acetate looks to change easily into another polymorph form. It means that VAL from n-butyl acetate was the metastable form among the polymorphs compared.
Fig. 4. X–ray diffractograms of (A) untreated VAL, (B) VAL from acetonitrile, (C) VAL from n-butyl acetate

Fig. 5. Monitored of polymorphic transformation within (A) grinding, (B) stored at RH 75%, and (C) RH 98% 

5. CONCLUSION

Phase transitions are usually neglected factors in the validation of manufactured products. These factors are common as hidden quality aspects. So, through this research, we want to introduce pharmacists who are concerned carefully. This study aims to obtain a polymorphic structure from acetonitrile and n-butyl acetate. These polymorphs have different properties, but for pharmaceutical development it shows that the VAL of n-butyl acetate has been handled with care, causing the shape to change easily.

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