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# Polymorphic form K of Pitavastatin calcium: an advance in stability and pharmaceutical applications

## Abstract

Pitavastatin's ability to effectively lower LDL-C and TG levels, while increasing HDL-C, has made it a potent option for lipid control. Polymorphism affects the drug's solubility, stability, and bioavailability, and while several polymorphic forms of pitavastatin calcium have been identified, including forms A, B, C, D, E, F, and amorphous forms, they present challenges in large-scale production due to sensitivity to processing conditions. Polymorphic form K overcomes these challenges, demonstrating superior chemical and physical stability under stress, high humidity, mechanical forces, and elevated temperatures. This form's low hygroscopicity improves storage and handling, making it a prime candidate for solid pharmaceutical formulations such as tablets and capsules. With remarkable resilience to degradation, polymorphic form K enhances both the shelf life and efficacy of pitavastatin-based medications, offering improved outcomes in the treatment of cardiovascular diseases.

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## Introduction

Hypercholesterolemia and mixed dyslipidemia are significant risk factors for cardiovascular diseases.[1] Statins are the cornerstone of lipid control treatment, with pitavastatin emerging as a potent option due to its effectiveness in reducing LDL-C and TG levels, as well as its ability to increase HDL-C levels over time.[2] Pitavastatin's innovative structure minimizes drug interactions, making it a favorable choice for patients on multiple medications.[3]

### Polymorphic forms of pitavastatin calcium

Polymorphism plays a crucial role in a compound's pharmaceutical properties, affecting its solubility, stability, and bioavailability. Various polymorphic forms of pitavastatin calcium have been reported, including forms A, B, C, D, E, F, and an amorphous form.[4–6]

I. **Form A:** Typically prepared by reacting sodium pitavastatin with calcium chloride in an aqueous medium. This form may contain up to 15% water, preferably between 3% and 12%. It is sensitive to drying conditions; inadequate drying can reduce the water content below 4%, decreasing its crystallinity and leading to instability.

II. **Forms B to F:** Derived from form A through different solvent treatments:

III. **Form B:** Obtained by suspending form A in ethanol with water as a co-solvent.

IV. **Form C:** Produced by suspending form A in isopropanol containing water or a mixture of isopropanol and a ketone solvent with water.

V. **Form D:** Prepared by suspending form A in absolute ethanol.

VI. **Form E:** Formed by suspending form A in 1,4-dioxane with water.

VII. **Form F:** Generated by suspending form A in methanol with water.

### Challenges of existing polymorphic forms

While these polymorphic forms are known, they present challenges for large-scale production.

**Polymorphic stability:** Different polymorphic forms can interconvert under varying conditions of temperature, humidity, and mechanical stress. This interconversion can lead to inconsistencies in the drug's efficacy and shelf life.

**Solubility variations:** Each polymorph has a unique solubility profile, affecting the drug's absorption rate. Inconsistent polymorph production can result in variable therapeutic outcomes.

**Sensitivity to processing conditions:** Factors such as solvent choice, temperature control, and crystallization techniques can influence which polymorphic form is produced. Small deviations in these parameters during large-scale manufacturing can lead to the unintended formation of less desirable polymorphs.

**Regulatory compliance:** Regulatory agencies require thorough characterization and control of polymorphic forms in pharmaceutical products. Inconsistencies can lead to compliance issues and potential recalls.

For instance, form A is highly sensitive to drying conditions, requiring precise control to avoid conversion into less stable forms or the amorphous state, which exhibits low storage stability.[4–6]

### The need for an improved polymorphic form

An ideal polymorphic form of pitavastatin calcium would be:

I. Stable under normal pharmaceutical processing conditions, such as drying, milling, granulation, and compression.

II. Scalable, with high yields and purity.

III. Resistant to conversion into other forms during processing and storage.

IV. Optimized for desirable physicochemical properties, including particle size distribution.

### Discovery of a new stable polymorphic form

Recent advances have led to the discovery of a new polymorphic form of pitavastatin calcium that meets these criteria. The polymorphic form K, developed through this new process, demonstrates exceptional chemical and physical stability, far surpassing other forms of pitavastatin calcium.[4–6] (Table 1)

**Table 1** XRD (2Θ angles) and water content of pitavastatin calcium polymorphs.[4–6]

| Polymorphs | XRD (2Θ angles) | Water Content |
|---|---|---|
| Form K | 3.8, 5.3, 1 1.3, 15.4, 17.4, 18.1, 19.2, 20.6, 22.3, 24.6. | 3.5939% |
| Form A | 5.0, 6.8, 9.1, 10.0, 10.5, 11.0, 13.3, 13.7, 14.0, 14.7, 15.9, 16.9, 17.1, 18.4, 19.1, 20.8, 21.1, 21.6, 22.9, 23.7, 24.2, 25.2, 27.1, 29.6, 30.2, 34.0. | 3 – 12% |
| Form B | 4.6, 5.3, 6.2, 7.7, 9.2, 9.6, 10.3, 11.3, 11.7, 12.6, 13.0, 13.9, 14.7, 14.9, 15.6, 16.3, 17.0, 17.4, 18.0, 18.7, 19.3, 20.0, 20.5, 20.8, 21.2, 21.5, 22.4, 23.2, 23.8, 24.4, 25.2, 26.0, 26.4, 27.0, 27.9, 28.9. | 1 – 50% |
| Form C | 4.1, 5.6, 7.8, 8.3, 10.3, 11.6, 17.5, 17.9, 18.7, 19.5, 20.6, 21.5, 21.9, 23.1, 24.0, 24.8. | 5% |
| Form D | 5.0, 6.5, 6.8, 8.7, 10.0, 10.2, 10.8, 13.1, 13.5, 14.3, 15.3, 16.1, 16.8, 18.2, 18.5, 19.0, 19.9, 20.5, 21.0, 21.7, 22.3, 23.4, 24.0, 25.6, 26.2. | - |
| Form E | 4.4, 5.0, 6.6, 6.8, 8.9, 10.0, 10.3, 10.8, 13.3, 13.6, 14.0, 15.2, 15.9, 16.4, 16.9, 17.8, 18.3, 18.9, 20.2, 20.4, 20.7, 20.9, 21.1, 21.6, 21.7, 22.3, 23.5, 23.8, 24.1, 24.7, 25.4, 26.6, 30.2, 34.0. | 1 – 50% |
| Form F | 5.1, 5.6, 7.0, 8.8, 9.6, 10.2, 10.9, 11.3, 11.9, 12.5, 13.0, 13.7, 14.4, 14.7, 15.3, 15.5, 16.8, 17.6, 18.3, 19.3, 19.7, 20.6, 21.2, 21.8, 22.8, 23.1, 23.8, 24.1, 24.8, 25.7, 26.2, 26.6, 26.9, 28.4, 29.5, 29.8, 30.9. | 1 – 50% |

## Stability under stress conditions

What makes polymorphic form K remarkable is its resilience under various stress conditions, where other forms typically degrade or transform into less stable states.[4–6] Through extensive testing, form K has maintained its stability under the following conditions:

**Stress stability conditions:** At 40°C and 75% relative humidity (RH) for one month, both in open and closed containers, form K remains stable.

**High humidity:** Even at 90% relative humidity at room temperature, over a period of three days, no changes were observed in its structure.

**Mechanical stress:** Subjected to a compression force of 8 tons/cm², it remains unchanged, retaining its crystalline form.

**Grinding:** When ground, for instance, in a mortar, the structure remains stable, unlike other polymorphic forms that can undergo significant changes under the same conditions (Figure 1).

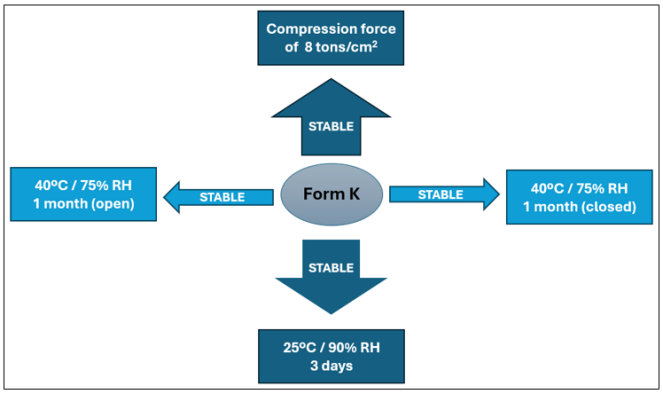


**Figure 1** Stability conditions of Form K.

## Thermal and chemical stability

One of the most impressive characteristics of polymorphic form K is its resistance to high temperatures. Compared to polymorphic form A, which decomposes around 180°C, form K only begins to decompose at temperatures above 248°C. This superior thermal stability is evident in differential scanning calorimetry (DSC) studies, where form K shows minimal changes even when heated to 220°C. In contrast, form A loses significant crystallinity and converts to an amorphous state at 180°C, making it less suitable for applications requiring heat resistance.[4–6]

Additionally, form K exhibits excellent chemical stability, outperforming both the amorphous form and other polymorphic forms of pitavastatin calcium. The amorphous form, while physically stable, is known to be chemically unstable, as evidenced by previous research. However, polymorphic form K remains stable both physically and chemically, making it a more reliable choice for pharmaceutical formulations.[4–6]

## Hygroscopic properties and packaging

Another important factor contributing to the practical usability of polymorphic form K is its low hygroscopicity. Unlike other forms of pitavastatin calcium, which are highly hygroscopic, form K absorbs significantly less moisture. This characteristic improves its storage and handling properties, reducing the risk of moisture-induced degradation.[4–6]

To preserve its stability, pitavastatin calcium in polymorphic form K can be packaged in materials such as polyethylene bags or hot-sealed laminated bags in an inert atmosphere, preferably with nitrogen. Storage is recommended at temperatures between 0°C and room temperature, ensuring further long-term stability.[4–6]

## Pharmaceutical applications

The unique stability of polymorphic form K offers significant advantages in the development of pharmaceutical compositions. It remains stable during standard processes used in drug manufacturing, such as granulation, compression, and drying, which are critical steps in the preparation of solid dosage forms like tablets and capsules.

Form K can be easily formulated into solid dosage forms through modern techniques such as direct compression, dry granulation, or wet granulation. These methods ensure that the drug remains stable and effective throughout the production process, resulting in high-quality and reliable medications.

# Conclusion

Polymorphic form K of pitavastatin calcium represents a significant advancement in pharmaceutical science, offering unmatched stability in both chemical and physical terms. Its resistance to stress, high temperatures, and humidity, along with its low hygroscopicity, makes it an ideal candidate for the development of solid pharmaceutical forms. As a result, form K not only extends the shelf life of medications but also enhances their reliability and efficacy in treating patients. This discovery promises to improve the production and formulation of cholesterol-lowering drugs, ensuring better outcomes for those at risk of cardiovascular diseases.

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## Conflict of interest

The authors declare that there is no conflict of interest.

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