Fuji Chemical Industries

Solving Puzzles since 1946.

Creativity and Contribution

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PHARMACEUTICAL NEWSLETTER

ELEVATING THE INNOVATOR STANDARD: OPTIMIZING STEGLUJAN®- TYPE FORMULATIONS WITH FUJICALIN®

FORMULATION CHALLENGES IN LOW-DOSE FIXED-DOSE COMBINATIONS

Developing fixed-dose combination (FDC) therapies presents unique formulation challenges, particularly when one active pharmaceutical ingredient (API) is present in a significantly lower dose than the other. Achieving content uniformity while maintaining chemical stability requires a strategic selection of excipients.

This newsletter explores the successful use of **Fujicalin®** (Dibasic Calcium Phosphate Anhydrous, DCPA) in the formulation of Steglujan® (sitagliptin and ertugliflozin), a commercialized product by MSD (Merck & Co., Inc.).

THE CHALLENGE: LOW-DOSE API AND STABILITY CONCERNS

Steglujan® is available in two strengths:

5 mg ertugliflozin / 100 mg sitagliptin

15 mg ertugliflozin / 100 mg sitagliptin

The significant difference in dosage between the two APIs presents a primary challenge:

1. Content Uniformity of Ertugliflozin: As a low-dose API (only 1.25% w/w in the 5 mg strength), ensuring that every tablet contains exactly the intended amount of ertugliflozin is critical.
Low-dose APIs are prone to segregation and poor distribution during the manufacturing process.

2.Nitrosamine Sensitivity: Sitagliptin is known to be prone to the formation of nitrosamine impurities. This requires the use of excipients with exceptionally low nitrite content to ensure long-term product safety and regulatory compliance.

3.Manufacturing Efficiency: A robust manufacturing process is essential for commercial success. Direct Compression (DC) is the preferred method for its efficiency and cost-effectiveness, but it requires excipients with excellent flow and compressibility.

THE SOLUTION: FUJICALIN® AS A PERFORMANCE-ENHANCING CO-DILUENT

To address these challenges, the innovator formulation for Steglujan® utilizes a combination of Microcrystalline Cellulose (MCC) and Dibasic Calcium Phosphate Anhydrous (DCPA), specifically leveraging the unique properties of **Fujicalin®**.

Why Fujicalin® (DCPA)?

Fujicalin® is a uniquely manufactured anhydrous dibasic calcium phosphate designed for direct compression. Its porous, spherical granules provide several key advantages for this specific FDC:

- ✓ SUPERIOR CONTENT UNIFORMITY
- ✓ LOW NITRITE CONTENT FOR STABILITY
- ✓ OPTIMAL FLOW AND COMPRESSIBILITY

- **Superior Content Uniformity:** The high surface area and porous structure of Fujicalin® allow it to act as a carrier for low-dose APIs. Ertugliflozin particles can be effectively "adsorbed" into the pores and onto the surface of the Fujicalin® granules, preventing segregation during blending and compression. This ensures highly consistent dosing across every tablet produced.
- **Low Nitrite Content for Stability:** Fujicalin® is manufactured with a focus on high purity. Its naturally low nitrite levels make it an ideal choice for nitrosamine-prone APIs like sitagliptin, helping to maintain the chemical integrity and safety of the final drug product throughout its shelf life.
- **Optimal Flow and Compressibility:** The spherical shape of Fujicalin® granules ensures excellent flowability, which is critical for high-speed direct compression. When used as a co-diluent with MCC, it provides the necessary tablet hardness and disintegration characteristics while maintaining a smooth, efficient production process.

INNOVATOR PRODUCT ANALYSIS: STEGLUJAN® (MSD)

According to the innovator's Orange Book listed patents[1], the formulation is carefully designed for stability and performance.

Core Tablet Composition:

- **Active Ingredients:** Ertugliflozin L-pyroglutamic acid and Sitagliptin phosphate monohydrate.
- **Key Excipients:** Microcrystalline cellulose (MCC), Dibasic calcium phosphate anhydrous (Fujicalin®), Croscarmellose sodium (disintegrant), Sodium stearyl fumarate, and Magnesium stearate (lubricants).

The manufacturing process for this innovator product utilizes Direct Compression (DC), followed by film coating and packaging. This streamlined process is made possible by the superior performance of the excipient blend.

PROPOSED FORMULATION STRATEGY

Based on the commercial success of Steglujan®, a tentative formulation for a similar sitagliptin/ertugliflozin tablet could be structured as follows:

Ingredients	Quantity (mg)	Percent w/w	Function
Sitagliptin base	100	25	Active Ingredient
Ertugliflozin eq.	5	1.25	Active Ingredient (Low Dose)
MCC	134.5	33.6	Diluent / Binder
Fujicalin® (DCPA)	134.5	33.6	Co-diluent for Content Uniformity
Croscarmellose sodium	20	5	Disintegrant
Sodium stearyl fumarate	2	0.5	Lubricant
Magnesium stearate	4	1	Lubricant
Total Tablet Weight	**400 mg**	**100%**	

Note: This formula is tentative and should be optimized based on specific API sources and equipment.

CONCLUSION: FUJICALIN® - THE IDEAL PARTNER FOR COMPLEX FDCS

The use of **Fujicalin®** in the innovator product Steglujan® serves as a powerful testament to its capabilities. By addressing the critical needs for content uniformity in low-dose APIs and providing a low-nitrite environment for sensitive molecules, Fujicalin® enables the development of high-quality, stable, and effective pharmaceutical products.

For formulators facing challenges with API distribution or stability, Fujicalin® offers a proven, commercially validated solution for direct compression success.

For further information, collaborative projects, or samples, Fuji Chemical Industries Co. Ltd. welcomes discussion with formulation scientists and business leaders.

For technical assistance, contact Fuji Chemical Industries Co. Ltd.'s technical support team at fist@fujichemical.co.jp

References:
1.US Patent No. 6699871, 6890898, 7078381, 7326708, 7459428, 8080580, 9308204, and 9439901

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