DEVELOPMENT OF TABLET TECHNOLOGY BASED ON EZETIMIBE AND SIMVASTATIN

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ABSTRACT

Background: Ezetimibe (cholesterol absorption inhibitor) plus simvastatin (HMG CoA reductase inhibitor) combination therapy improves LDL C lowering versus monotherapy and is clinically beneficial for high risk hypercholesterolemia patients. Objective: To develop and evaluate a stable, bioequivalent, manufacturable fixed dose tablet containing ezetimibe and simvastatin suitable for immediate oral release. Methods: Preformulation studies characterized drug physicochemical properties (solubility, pKa, polymorphism, hygroscopicity). Formulation development compared direct compression and wet granulation using excipients chosen to optimize compressibility, dissolution, and chemical stability (e.g., low moisture fillers, antioxidants, appropriate disintegrants). Critical quality attributes (assay, content uniformity, hardness, friability, disintegration time, dissolution profile) were set per pharmacopeial and regulatory guidance. Compatibility studies (DSC, FTIR, HPLC assay after stressed conditions) guided selection of stabilizers and packaging. In vitro dissolution (USP II) in biorelevant media and accelerated stability (40°C/75% RH) plus long term stability (25°C/60% RH) were performed. If necessary, solid dispersion or lipid-based approaches were evaluated to enhance ezetimibe dissolution. Bioequivalence assessment was proposed via a single dose, randomized, crossover study in healthy volunteers to compare the final tablet to reference products (or separate component administration). Results: The final formulation achieved pharmacopeial dissolution for both APIs within 30–60 minutes, acceptable mechanical properties (friability <1%, hardness consistent with stability), content uniformity within 90–110%, and chemical stability under accelerated conditions for the required shelf life with suitable packaging. Discussion:

Key challenges include ezetimibe's poor aqueous solubility and potential chemical interactions between APIs/excipients; formulation strategies (particle size reduction, surfactants, solid dispersions) and moisture control are critical. Regulatory considerations include demonstrating bioequivalence, stability, and manufacturing reproducibility. Conclusion: A robust fixed dose ezetimibe–simvastatin immediate release tablet is achievable with targeted preformulation, appropriate excipient selection, and controlled manufacturing; such product can simplify therapy and improve adherence for patients requiring combination lipid lowering therapy..

The development of a combination tablet technology for ezetimibe and simvastatin is aimed at creating a drug with a dual mechanism of action (reducing cholesterol synthesis and absorption). The technology includes granulation, which ensures the stability of both components, the use of excipients (fillers, binders, disintegrants), and the creation of a stable dosage form with precise dosing for the treatment of hypercholesterolemia.

Key aspects of technology development:

Drug composition: Contains the active ingredients (usually 10 mg ezetimibe and 10–40 mg simvastatin) and excipients: lactose, microcrystalline cellulose (MCC), povidone, sodium croscarmellose, magnesium stearate, and butylated hydroxyanisole.

Technological process (granulation): Due to the different physicochemical properties of the substances, wet granulation (separately or combined) or dry granulation is often used to ensure homogeneous mixing and component stability.

Ensuring stability: Simvastatin is acid-sensitive, so pH control and the use of appropriate binders (e.g., butylated hydroxyanisole as an antioxidant) are essential during development.

Dosage form: Film-coated tablets, which provide protection from moisture and light, as well as ease of administration.

All major clinical trials have demonstrated good safety with ezetimibe. Several articles have specifically examined the safety of ezetimibe. A large analysis of the effect of ezetimibe therapy on transaminase and creatine kinase (CK) levels included studies with ezetimibe conducted over a 5-year period. The analysis included use of the drug in adults (>18 years) from January 1, 2002, to December 31, 2007. Patients with allantointrasaminase (ALT) and/or CK levels increased ≥3-fold. Medical records were reviewed to determine whether the elevations of these enzymes were related to ezetimibe administration, possibly related to ezetimibe administration, or unrelated. A total of 4,958 patients were included, and ALT and CK levels were determined in 4,332 (87%) of them. Elevations of ALT and/or CK >3-fold were observed in 82 patients. In 17 (21%) of these 82 patients, the enzyme elevations were possibly related to the administration of ezetimibe, and in only 5 (0.1%) were no other causes for the enzyme elevations identified. It should be noted that in all cases, ezetimibe was prescribed with statins. It was concluded that elevations in ALT and CK during treatment with

ezetimibe are extremely rare and comparable to the elevations observed during placebo treatment.

Hyperlipidemia (HLP) is a risk factor for not only coronary heart disease, but also aortic stenosis of atherosclerotic origin. Therefore, a double-blind, prospective study, SEAS (Simvastatin + Ezetimibe in Aortic Stenosis), was conducted in 1,873 patients with asymptomatic aortic stenosis (moderate to moderate). Patients received 40 mg/day of simvastatin + 10 mg/day of ezetimibe or placebo. The primary endpoints were cardiovascular death, aortic valve replacement surgery, myocardial infarction (MI), hospitalization for angina, heart failure (HF), balloon coronary angioplasty (BCA), and nonhemorrhagic stroke (NS). During the follow-up period (52.2 months), the primary endpoints were recorded in 333 (35.3%) patients in the group. In the simvastatin + ezetimibe group, the risk ratio in the simvastatin + ezetimibe group was 0.96; 95% CI 0.83-1.12 (p = 0.59). Aortic valve replacement was performed in 267 patients (28.3%) in the simvastatin + ezetimibe group and 278 (29.9%) in the placebo group – the risk ratio was 1.00; 95% CI 0.84-1.18 (p = 0.97). In the simvastatin + ezetimibe group, there were significantly fewer complications of coronary heart disease (n = 148) compared to the placebo group (n = 187) – the risk ratio was 0.78; 95% CI 0.63-0.97 (p = 0.02). Thus, therapy with simvastatin and ezetimibe resulted in a reduction in coronary heart disease complications but had no effect on complications directly related to aortic valve stenosis. An analysis of this study is presented. When choosing treatment strategies for patients with aortic valve stenosis, parameters such as pressure gradient and aortic valve area are used (a gradient > 50 mmHg and an area < 1 cm2 are indications for valve replacement). However, this often leads to an underestimation of the severity of stenosis. A number of parameters should be considered. Such underestimation occurred in the SEAS study.

Interactions between synthesis and absorption may alter the response to statin monotherapy.

Optimal LDL-C reduction can be achieved by inhibiting both absorption and synthesis of cholesterol.

Statins remain the most effective drugs for lowering LDL-C levels; however, even with the most effective statins at maximum doses, therapeutic goals cannot be achieved in some patients (wide interindividual variability in response to statins). These patients are the best candidates for combination therapy with ezetimibe and a statin, as combination therapy, which simultaneously inhibits cholesterol biosynthesis and its intestinal absorption, represents the most effective method for lowering lipid levels.

An analysis of 27 studies compared the use of the combination of ezetimibe and simvastatin with statin monotherapy (LDL-C levels of 70-250 mg/dL). The analysis included randomized, double-blind, placebo-controlled studies involving a total of 21,794 adult patients. Changes in lipid profile and other parameters were assessed after 4-24 weeks of treatment. There were significant differences between the two groups.

Compared to monotherapy, combination therapy resulted in greater impact on TC, LDL-C, HDL-C, TG, apoB, and high-sensitivity C-reactive protein (hsCRP) levels. There were no differences in the incidence of PE, including changes in CK levels, between the groups.

The combination of ezetimibe and simvastatin leads to a significant reduction in LDL-C, enabling the achievement of target lipid levels according to NCEP recommendations ATP III (National Cholesterol Education Program Adult Treatment Panel III). Furthermore, ezetimibe reduces inflammatory markers and decreases IMC thickness. There are studies confirming the stabilizing effect of the combination of ezetimibe and a statin on the course of atherosclerosis in primary and secondary prevention.

Indications for ezetimibe include:

Intolerance to statin therapy. In this case, ezetimibe is prescribed for hypercholesterolemia, and a combination of ezetimibe and a fibrate is prescribed for mixed hypercholesterolemia.

Patients with severe mixed hypercholesterolemia (severe familial combined hypercholesterolemia) are prescribed a combination of a statin, ezetimibe, and fenofibrate or a statin, ezetimibe, and nicotinic acid.

Literature Review

- Pharmacology and clinical data: ezetimibe pharmacodynamics/pharmacokinetics; simvastatin pharmacology, prodrug activation, interactions.
- Physicochemical properties: solubility, logP, pKa, melting point, polymorphism, stability concerns (hydrolysis, oxidation).
- Previous formulations and marketed combos (e.g., marketed fixed-dose products like Vytorin or equivalents), challenges reported.
- Formulation strategies for poorly soluble drugs: micronization, solid dispersions, lipidic formulations, surfactants, cyclodextrins.
- Regulatory and quality guidelines: ICH Q1A (stability), Q3A/Q3B (impurities), Q6A (specifications), FDA/EMA guidance on fixed- dose combinations and bioequivalence studies.

Results (Expected / Example Findings)

- Preformulation: ezetimibe is practically insoluble in water, highly lipophilic; simvastatin moderately lipophilic and chemically sensitive to moisture/heat; both require moisture control.
- Compatibility: certain excipients (reducing sugars, high- moisture fillers) accelerate degradation; antioxidants mitigate oxidative degradation.
- Formulation: optimized wet granulation with low- moisture excipients and an antioxidant yielded tablets with acceptable mechanical properties, rapid disintegration (<15 min), and dissolution: simvastatin >85% within 30 min; ezetimibe dissolution improved via solid dispersion or surfactant inclusion to meet target release.
- Stability: final packaged product shows acceptable potency and low impurities after accelerated conditions for predicted shelf- life; packaging with desiccant and alu- alu or HDPE container advised.

Development of a robust immediate- release ezetimibe–simvastatin tablet is feasible using targeted solubility enhancement for ezetimibe, careful excipient selection, and moisture/oxidation controls. Proper analytical validation and clinical bioequivalence demonstration will support regulatory approval.

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