INTRODUCTION
Pravastatin is a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor that lowers serum cholesterol levels and reduces cardiovascular risk [1]. Statin-based drugs are actively recommended when patients with increased cholesterol have high blood pressure, diabetes, and cardiovascular disease [2]. Following oral administration, pravastatin reaches maximum plasma concentration (Cmax) after approximately 0.88–1.00 h and has a half-life of 1.97–2.15 h and 18% bioavailability [3]. Ezetimibe inhibits Niemann-Pick Cl-Like one protein affecting intestinal cholesterol absorption [4]. Ezetimibe reaches Cmax at approximately 1.00–2.00 h after oral administration; its half-life is approximately 22.00 h with low and high oral bioavailability of 35% and 65%, respectively [5,6].

Fixed-dose combination (FDC) tablets include various additives such as excipients, binders, disintegrants, and lubricants besides the active pharmaceutical ingredient (API) to ensure adequate absorption, improve appearance, and increase stability. According to the general rule of the Korean Pharmacopoeia, appropriate additives such as excipients, stabilizers, preservatives, and buffering agents may be added to the formulation, unless otherwise stipulated, to secure quality and enhance efficacy. All additives should be harmless to the API dose and should not modify its therapeutic effect. Therefore, when formulating pharmaceuticals, additives should be selected considering their stability, safety, and quality. However, there may be interactions between the API and additives, such as complex formation or acid-base reactions, which may affect stability, dissolution rate, solubility, and bioavailability [7]. Thus, the study of potential physical and chemical interactions between drugs and excipients is an important step in the formulation process [8]. The recent International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on pharmaceutical development encourages the manufacture of stable medicines using the quality by design (QbD) approach [9]. In Korea, QbD is applied to each formulation step in the formulation process [8]. The recent International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on pharmaceutical development encourages the manufacture of stable medicines using the quality by design (QbD) approach [9]. In Korea, QbD is applied to each formulation step in the formulation process [8].

Thus, the purpose of this study was to investigate the compatibility of the excipients used in the development of a pravastatin and ezetimibe FDC tablet using high-performance liquid chromatography (HPLC), X-ray diffraction (XRD), differential scanning calorimetry (DSC), and thermogravimetric (TG) analysis. The excipients tested include lactose monohydrate, microcrystalline cellulose, magnesium oxide, hydrated ferric oxide, croscarmellose sodium, magnesium stearate, sodium lauryl sulfate, and polyvinylpyrrolidone.

MATERIALS AND METHODS
Materials
Pravastatin (>99% purity) was supplied by Guangdong Blue Treasure Pharmaceutical Co., Ltd. (Guangdong, China). Ezetimibe (>99% purity) was supplied by Neuland Laboratories Limited (Andhra Pradesh, India). The excipients lactose monohydrate (Pharmatose 101, DMV, India), croscarmellose sodium (Acdisol®), magnesium stearate (Hyqual®, Daechi Sankyo Co., Ltd., Japan), and Ezetimibe were Ezetrol® (Merck, India). The reference formulation of pravastatin was Mevakin® (Daiichi Sankyo Co., Ltd., Japan).

Drug-excipient compatibility study
To assess compatibility, pravastatin, ezetimibe, and pharmaceutical excipients were mixed at an arbitrary weight ratio to confirm the stability of the interaction [10,11]. The excipients were used in a similar manner to that in the Mevalotin® and Ezetrol®. Table 1 shows the test conditions for the compatibility study. Table 2 describes the ratios of the binary mixtures and whole and partial blends that were prepared to identify the interactions between the drugs (pravastatin and ezetimibe) and excipients [12]. The expected pravastatin and ezetimibe FDC tablet was double-layered and formulated through wet granulation (PG) (Table 3).
All mixtures were prepared to form dry powders and were packed using Alu-Alu foil.

**Impurity test**

The impurities of pravastatin and ezetimibe were assessed using the Agilent 1100 series HPLC system (Agilent Technologies, USA). HPLC analysis for pravastatin was performed using a C18 column (Zorbax SB-C18, 4.6 × 150 mm, 3.5-μm particle size, Agilent Technologies). The mobile phase was injected by gradient elution and consisted of solvent A (distilled water: phosphate buffer [pH adjusted to 7.0 with trimethylamine in 0.08 mol/L phosphoric acid]:acetonitrile at 520:300:180 v/v/v) and solvent B (acetonitrile: phosphate buffer [0.08 mol/L, pH 7.0]:distilled water at 600:300:100 v/v/v) at a flow rate of 0.1 mL/min. The initial mobile phase composition was maintained at 100% solvent A for 3.00 min, changed linearly to 0% (3.00–26.50 min), and maintained for 3.40 min (26.60–30.00 min) for column equilibrium. The analysis time and detection wavelength were 45 min and 235 nm, respectively. The standard stock solution was prepared by dissolving 12.5 mg of pravastatin 1,1,3,3-tetramethylbutylamine standard in 100 mL of 50% methanol. Then, 1.0 mL of this solution was diluted in 100 mL of 50% methanol, which was used as the standard solution. To prepare sample solution, 50 mg of pravastatin was placed in a 100-mL volumetric flask, to which 50% methanol was added; the flask was then shaken for 15–20 min in an ultrasonic shaker. Oxidation impurities, 6'-epipravastatin, pravastatin lactone, and other individual impurities, and total impurities as well as all total impurities were identified [13].

HPLC analysis for ezetimibe was performed using a C18 column (Pursuit XR Cs, 250 × 4.6 mm, 5-μm particle size, Agilent Technologies). The mobile phase included gradient elution of acetoniitrile and buffer (0.05% w/v 1-heptanesulfonic acid sodium salt in 1000 mL of distilled water, adjusted to pH 6.8 with 0.04% Na2CO3 solution). The mobile phase consisted of solvent A (0.05% w/v 1-heptanesulfonic acid sodium salt buffer [pH 6.8]) and solvent B (acetoniitrile) injected at a flow rate of 1.5 mL/min. The initial mobile phase composition was maintained at 70% solvent A, changed linearly to 60% (0.00–6.00 min), 55% (6.00–16.01 min), and 10% (16.01–28.00 min), then maintained at 10% (28.00–30.00 min), again changed linearly to 70% (30.00–30.01 min), and maintained for 10 min (30.01–40.00 min) for column equilibrium. The analysis time and detection wavelength were 45 min and 235 nm, respectively. For the standard solution, 25-mg ezetimibe standard was transferred to a 50 mL volumetric flask, dissolved in 20 mL of diluent solvent A; solvent B = 4.6L; made up to the required volume with diluent and shaken for 15–20 min in an ultrasonic shaker.

**Impurity-A, Impurity-B, Impurity-C, Impurity-D, and other individual impurities were identified on chromatograms [14].**

**XRD analysis**

Diffractograms were obtained using an automated multipurpose X-ray diffractometer (SmartLab, Rigaku, Japan) with Cu-Kα radiation (40 kV, 40 mA) in the range of 5–40° [20] [15].

**DSC and TG**

DSC and TG were performed using a heat flux plate-type calorimeter (DSC 131 EVO, Setaram Instrumentation, France) and a thermobalance (N-1500, SCINCO, South Korea), respectively, at a temperature of 25–350°C. Samples of approximately 4 mg were assessed under nitrogen gas at a flow rate of 30 cc/min and a heating rate of 10°C/min.

**Statistical analysis**

Mean±standard deviation for all experimental results was evaluated using the SAS Software (Ver: 9.4, SAS Institute Inc., Cary, NC, USA).

**RESULTS**

**Drug-excipient compatibility**

The impurity content of pravastatin and ezetimibe changed when mixed with excipients. The accelerated test results of pravastatin indicated that all excipients except the PL, PC, PP, and PS samples (Table 2) of lactose monohydrate, crosscarmellose sodium, polyvinylpyrrolidone, and sodium lauryl sulfate, respectively, were found to slightly increase total impurity (Table 4). The accelerated test results of ezetimibe indicated that except for the EM2, EP, and EO samples (Table 2) of magnesium oxide, polyvinylpyrrolidone, and ezetimibe only, other excipients did not increase total impurity (Table 5). However, all observed impurity results were below the acceptance criteria, as shown in Tables 4 and 5.

**Powder XRD analysis**

The XRD curves of drugs and excipients (Table 2) revealed characteristic peaks showing crystalline forms. The XRD patterns of pravastatin and ezetimibe (Fig. 1) showed sharp, intense, and less diffused peaks at 20 angles (pravastatin: 4.1–24.4° and ezetimibe: 13.62–29.59°), indicating

**Table 1: Summary for the compatibility study of pravastatin and excipients**

| Test items                  | Conditions                                                                 |
|-----------------------------|-----------------------------------------------------------------------------|
| Stability-indicating method | Qualitative analysis by HPLC (impurity), DSC-TG, and description (visual)   |
| Storage condition           | Accelerated (40°C/75% Relative humidity)                                    |
| Closure system (open or closed) | Alu-Alu (closed)                                      |
| Test period                 | 4 weeks (sampling time=0, 2, and 4 weeks)                                   |
| Mixing method               | Binary mixtures, whole and partial blends                                   |

*Differential scanning calorimetry and Thermogravimetric analysis. HPLC: High-performance liquid chromatography, DSC: Differential scanning calorimetry, TG: Thermogravimetric

**Table 2: Samples for drug-excipient compatibility study**

| Drug substance (A) | Excipients (B) | Samples | A:B ratio (Pravastatin) | A:B ratio (Ezetimibe) |
|--------------------|----------------|---------|-------------------------|----------------------|
| Pravastatin sodium | Lactose monohydrate | PL, EL | 1 | 10 |
| (P) and Ezetimibe (E) | Microcrystalline cellulose | PM1, EM1 | 1 | 4 |
| | Magnesium oxide | PM2, EM2 | 2 | 1 |
| | Hydrated ferric oxide | PH, EH | 200 | 1 |
| | Crosscarmellose sodium | PC, EC | 1 | 4 |
| | Polyvinylpyrrolidone | PP, EP | 5 | 1 |
| | Sodium lauryl sulfate | PS, ES | 2 | 1 |
| | Magnesium stearate | PM3, EM3 | 4 | 1 |
| Pravastatin granule after wet PG | PG | N/A |
| Ezetimibe granule after wet PG | EG | N/A |
| Pravastatin total mixture | PTM | N/A |
| Ezetimibe total mixture | EMT | N/A |
| Pravastatin only | PO | N/A |
| Ezetimibe only | EO | N/A |

*Pravastatin wet granulation is mixed and performed by ingredients of No. 1-5. *Ezetimibe wet granulation is mixed and performed by ingredients of No. 1, 2, 5, 6, and 7. *Pravastatin total mixture is performed by ingredients of No. 1-5, and 8. *Ezetimibe total mixture is performed by ingredients of No. 1, 2, 5, and 6-8. The composition of pravastatin and ezetimibe wet granulation and total mixture is as Table 3. PG: Granulation

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the high crystalline form of pure pravastatin (PO sample) (Fig. 1a) and ezetimibe (EO sample) (Fig. 1b). After maintaining accelerated condition (40°C. 65% relative humidity) for 4 weeks (Fig. 1c and d), the diffraction patterns of the drugs and excipients showed several peaks similar to the original form, indicating that the crystallinity of pravastatin and ezetimibe remained unchanged (Fig. 1).

**DSC and TG**

The results of DSC and TG of pravastatin (PO sample of Table 2) and ezetimibe (EO sample of Table 2) in Alu-Alu foil under accelerated conditions are illustrated in Fig. 2. The initial DSC curve of pravastatin showed the first endothermic event between 174 and 188°C ($\Delta H_{onset} = 1.394 \text{ J}$), with a melting temperature of $T_{onset}$ of 174°C (Fig. 2a). The TG curve exhibited 42.57% mass loss between 249 and 385°C with the decomposition of pravastatin (Fig. 2c). The DSC curve of pravastatin after 4 weeks showed the first endothermic event between 166 and 179°C ($\Delta H_{onset} = 1.079 \text{ J}$), with a melting temperature of $T_{onset}$ of 166°C (Fig. 2a). The TG curve exhibited 41.13% mass loss between 251 and 388°C with the decomposition of pravastatin (Fig. 2c).

The initial DSC curve of ezetimibe showed the first endothermic event between 162 and 173°C ($\Delta H_{onset} = 2.769 \text{ J}$), with a melting temperature of $T_{onset}$ of 162°C (Fig. 2b). The TG curve exhibited 90.38% mass loss between 190 and 392°C (Fig. 2d). The DSC curve of ezetimibe after 4 weeks showed the first endothermic event between 161 and 170°C ($\Delta H_{onset} = 1.079 \text{ J}$), with a melting temperature of $T_{onset}$ of 161°C (Fig. 2b). The TG curve exhibited 89.19% mass loss between 202 and 394°C (Fig. 2d).

**DISCUSSION**

This study tested the compatibility of excipients used in a bi-layer FDC tablet of pravastatin and ezetimibe. The total weight of Ezetrol® (ezetimibe) 10 mg tablet was 100 mg and of Mevalotin® (pravastatin) 40 mg was 400 mg. The total weight of the ezetimibe layer for the FDC tablet retained the same amount as Ezetrol® 10 mg. However, 200 mg of the total weight of the pravastatin layer was used to improve dose compliance. An understanding of compatibility is an integral part of the pre-formulation stage to assess safety, therapeutic properties, and stability of the dosage form. Hence, compatibility of pravastatin and ezetimibe of the bi-layer tablet should be studied with the excipients used in the other layer [16]. General excipients were used in this study to identify their stability.

**Table 3:** The expected formulation of pravastatin and ezetimibe layers

| Ingredient             | Pravastatin formulation (mg) | Ezetimibe formulation (mg) |
|------------------------|------------------------------|----------------------------|
| Pravastatin            | 4.00                         | -                          |
| Ezetimibe              | -                            | 10.00                      |
| Lactose monohydrate    | 9.10                         | 43.50                      |
| Microcrystalline cellulose | 19.80                     | 20.00                      |
| Magnesium oxide        | 7.00                         | -                          |
| Hydrated ferric oxide  | 0.20                         | -                          |
| Polyvinylpyrrolidone   | 1.000                        | 2.00                       |
| Sodium lauryl sulfate  | -                            | 4.00                       |
| Croscarmellose sodium  | 3.000                        | 20.00                      |
| Magnesium stearate     | 2.00                         | 0.50                       |
| Total                  | 20.00                        | 100                        |

**Table 4:** Compatibility results on each binary and all mixture of pravastatin with excipients under 40°C/75% relative humidity condition

| Samples | Time (Weeks) | Oxidation impurity (<1%) | Impurity B (<0.3%) | Pravastatin lactone (<2%) | Any other individual impurity (<0.2%) | Total impurity (<0.5%) | Description |
|---------|--------------|--------------------------|-------------------|---------------------------|---------------------------------------|------------------------|-------------|
| PL      | 0            | <RT*                     | <RT               | <RT                       | <RT                                   | <RT                    | White or off white powder |
| PM1     | 0            | <RT                      | <RT               | <RT                       | <RT                                   | <RT                    | White or off white powder |
| PM2     | 0            | <RT                      | <RT               | <RT                       | <RT                                   | <RT                    | White or off white powder |
| PH      | 0            | <RT                      | <RT               | <RT                       | <RT                                   | <RT                    | Light brown powder         |
| PC      | 0            | <RT                      | <RT               | <RT                       | <RT                                   | <RT                    | White or off white powder |
| PP      | 0            | <RT                      | <RT               | <RT                       | <RT                                   | <RT                    | White or off white powder |
| PS      | 0            | <RT                      | <RT               | <RT                       | <RT                                   | <RT                    | White or off white powder |
| PM3     | 0            | <RT                      | <RT               | <RT                       | <RT                                   | <RT                    | White or off white powder |
| PG      | 0            | <RT                      | <RT               | <RT                       | <RT                                   | <RT                    | White or off white powder |
| PTM     | 0            | <RT                      | <RT               | <RT                       | <RT                                   | <RT                    | White or off white powder |

*Reporting thresholds (0.1%)
Although, some excipients can have minor effects on pravastatin 0.13±0.006, 0.05±0.009, 0.11±0.006, and 0.08±0.001%, respectively, with values of total impurity after 4 weeks (Table 5). Ezetimibe oxide and polyvinylpyrrolidone in the EM2 (0.18±0.009%) and EP results showed low-level interactions except with magnesium observed as lumps and did not exhibit browning (Table 4). Ezetimibe and ezetimibe impurities changed when mixed with excipients.

Therefore, incompatible combinations are generally excluded during formulation development [16]. As shown in Tables 4 and 5, pravastatin and ezetimibe impurities changed when mixed with excipients. Some incompatible combinations of general excipients with known functional groups and their reactions are as follows: primary amine and mono- and disaccharides (amine-aldehyde or amine-acetal reactions); ester, cyclic, lactose, and basic compounds (ring-opening, ester-base or hydrolysis reactions); carbonyl, hydroxyl, and silanol (hydrogen bonding reactions); aldehyde, amine, and carbohydrates (aldehyde-amine, Schiff base or glycosylamine formation reactions); carbonyl and bases (salt formation reactions); alcohol and oxygen (oxidation of aldehydes and ketones); sulhydryl and oxygen (dimetization reactions); phenol and metals (complexation reactions); and gelatin capsule and cationic surfactants (denaturation reactions). In this study, chemical stability between the drugs pravastatin and ezetimibe and excipients was evaluated by HPLC under accelerated conditions (40°C this study, chemicals for 4 weeks. XRD, DSC, and TG were used to assess the physical stability of pravastatin and ezetimibe [19].

The crystal form determined using XRD analysis was directly assessed to identify the stability of the drugs (pravastatin and ezetimibe) with mixed excipients by plotting intensity versus the diffraction angle (2θ) (Fig. 1). The results confirmed a single crystal form of pravastatin (PO sample) and ezetimibe (EO sample) [6,20]. The XRD analysis of drugs mixed with excipients demonstrated some characteristic peaks without unaltered drug peaks, indicating that a homogeneous mixture was achieved under accelerated conditions (40°C this study, chemicals for 4 weeks. XRD, DSC, and TG were used to assess the physical stability of pravastatin and ezetimibe [19].

DSC or thin layer chromatography (TLC) is commonly used to select excipients. Moreover, excipients are selected for formulation studies if they show no interactions with the drug according to DSC results [17,18]. However, the DSC method is not sensitive to small changes, cannot confirm the effects of various environmental factors, and confirming long-term stability is difficult. Thus, decomposition products that cannot be identified using DSC are identified using TLC [17]. In this study, chemical stability between the drugs pravastatin and ezetimibe and excipients was evaluated by HPLC under accelerated conditions (40°C this study, chemicals for 4 weeks. XRD, DSC, and TG were used to assess the physical stability of pravastatin and ezetimibe [19].
Fig. 1: Powder X-ray diffraction results on (a) pravastatin (initial), (b) ezetimibe (initial), (c) pravastatin (after 4 weeks), and (d) ezetimibe (after 4 weeks) under 40°C/75% relative humidity condition. The name of samples is same as Table 2.

Fig. 2: Differential scanning calorimetry (DSC) and thermogravimetry (TG) curves of pravastatin and ezetimibe stored at accelerated (40°C/75% Relative humidity) for initial (a) and (c) DSC (a for pravastatin and c for ezetimibe) and TG (e for pravastatin and g for ezetimibe), and after 4 weeks (b) and (d) DSC (b for pravastatin and d for ezetimibe) and TG (f for pravastatin and h for ezetimibe).
analyzing and comparing physico-chemical interactions between drugs and excipients [23]. To determine the chemical stability of pravastatin and ezetimibe, their thermoanalytical profiles were identified by DSC and TG under accelerated conditions (40°C/75% relative humidity) using initial and 4-weeks samples in Alu-Alu foil (PO and EO samples; Table 2). DSC and TG of pravastatin and ezetimibe in Alu-Alu foil for 4 weeks demonstrated no change in their thermoanalytical patterns (Fig 2).

CONCLUSION
In this study, excipients compatible with pravastatin and ezetimibe were identified by impurity testing, XRD, DSC, and TG. We found that lactose monohydrate; croscarmellose sodium, polyvinylpyrrolidone, sodium lauryl sulfate, and magnesium oxide were slightly affected by the impurities of pravastatin and ezetimibe and were within acceptance ranges of total impurity. According to the results of XRD, DSC, and TG, the applicability of pravastatin and ezetimibe FDC tablets was demonstrated by a preformulation study. All excipients used in this study were compatible with pravastatin and ezetimibe. This study concluded that the tested excipients can be used for formulating pravastatin and ezetimibe FDC tablets.

AUTHOR’S CONTRIBUTIONS
Prof. K. M. Kim performed experiments, interpreted data, wrote the manuscript, and acted as corresponding author.

CONFLICTS OF INTERESTS
Authors have none to declare.

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