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Application of Quasi-Emulsion Solvent Diffusion for Spherical Crystallization of Atorvastatin with HPMC E50

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Abstract

Poor solubility and inadequate flowability of active pharmaceutical ingredients are significant challenges in developing solid oral dosage forms, particularly for BCS Class II drugs such as atorvastatin calcium. This study aimed to improve the micromeritic and dissolution properties of atorvastatin through spherical crystallization using quasi-emulsion solvent diffusion. Methanol was used as a good solvent, dichloromethane as a bridging liquid, water as a poor solvent, and HPMC E50 as a polymeric stabilizer. Spherical agglomerates were prepared and characterized for morphology (SEM); crystallinity (DSC and PXRD); chemical compatibility (FTIR); micromeritic parameters; and dissolution performance. The crystallization process transformed irregular atorvastatin crystals into smooth spherical agglomerates with significantly enhanced flow properties, as evidenced by increased flow rate and improved angle of repose, bulk density, and compressibility index. FTIR analysis confirmed no chemical interaction with HPMC, while PXRD and DSC indicated reduced crystallinity. Dissolution studies showed spherical atorvastatin exhibited superior release, reaching over 80% in 30 minutes, compared with 51% for raw atorvastatin. In conclusion, spherical crystallization effectively improved the physicochemical and micromeritic properties of atorvastatin calcium, offering a promising approach for enhancing its manufacturability and oral bioavailability.

Keywords: Spherical crystallization; Atorvastatin calcium; Micromeritic properties; Dissolution enhancement.

INTRODUCTION

The formulation of poorly water-soluble active pharmaceutical ingredients (APIs) remains a significant challenge in drug development. Many APIs, particularly those classified under the Biopharmaceutical Classification System (BCS) Class II, exhibit high permeability but low aqueous solubility, limiting their oral bioavailability and therapeutic effectiveness. Enhancing the solubility and processability of such compounds has become a key focus in pharmaceutical research (Kardum et al., 2023; Veith et al., 2021). Among the various strategies developed, crystal engineering has gained prominence for modifying particle morphology to improve performance in downstream processing.

Spherical crystallization has emerged as a powerful technique that transforms irregular crystals into spherical agglomerates through controlled crystallization, improving flowability, compressibility, and dissolution rates. Compared to traditional crystal forms, spherical agglomerates exhibit better packing and reduced interparticle friction, thus supporting efficient tablet production (Thenge et al., 2020). Kosnik et al. (2025) demonstrated the scalability of this method in a pilot plant study, confirming its suitability for industrial application.

Recent advancements have introduced variations of spherical crystallization, including quasi-emulsion solvent diffusion (QESD) and bridging liquid techniques, to enhance control over particle size and morphology. These methods benefit from improved reproducibility and allow the production of tailored particles for specific release profiles (Sun et al., 2024; D. Wang et al., 2024). Computational approaches, such as machine learning-assisted process optimization, have also been explored to predict optimal crystallization conditions (Ma et al., 2021).

The use of excipients during crystallization, particularly hydrophilic polymers like hydroxypropyl methylcellulose (HPMC), has been shown to enhance agglomerate stability. Gupta et al. (2023) developed a crystallo-co-agglomeration approach using HPMC to promote robust agglomerate formation, reduce processing steps, and improve tablet strength. HPMC also stabilizes metastable forms and improves handling characteristics.

Atorvastatin calcium, a widely prescribed statin, is a BCS Class II drug characterized by poor solubility and flowability. These limitations complicate its formulation and often necessitate multistep granulation processes. Spherical crystallization offers a more efficient alternative by producing directly compressible agglomerates with enhanced micromeritic properties (Pitt et al., 2018; Xiao et al., 2021). Chen et al. (2019) reported that spherical crystals of griseofulvin displayed significantly better dissolution profiles and tabletability.

A promising solvent system, relevant for applying these techniques to atorvastatin, includes methanol (good solvent), dichloromethane (bridging liquid), and water (poor solvent). Parvaresh et al. (2024) demonstrated that the sequential addition of these solvents, in combination with HPMC E50, led to improved agglomerate formation and particle stability. HPMC E50 increases the medium's viscosity, controls crystal growth, and helps retain spherical shape (Chen et al., 2019b). Early addition of HPMC as part of the bridging phase enhances cohesion and uniformity of agglomerates (S. Wang et al., 2018; L. Zhang et al., 2021).

Despite promising results, few studies have systematically evaluated the combined effects of this ternary solvent system and HPMC E50 on the pharmaceutical performance of atorvastatin. Most research has addressed solubility or mechanical properties separately, leaving a gap in comprehensive evaluations of the suitability of direct compression. The present study aims to investigate how spherical crystallization of atorvastatin calcium using methanol, dichloromethane, water, and HPMC E50 influences flowability, compressibility, and dissolution. This work seeks to establish an efficient, scalable formulation platform aligned with modern manufacturing demands.

MATERIALS AND METHODS

Materials

The materials used in this study include atorvastatin calcium pharmaceutical grade (Hubei Gedian Humanwell Pharmaceutical Co., Ltd., China), methanol pro-analysis (p.a) grade (Merck, Germany), dichloromethane p.a (Merck, Germany), and hydroxypropyl methylcellulose (HPMC) E50 pharmaceutical excipient grade (Dow Chemical Company, USA). Distilled water (aquadest) was obtained from PT Brataco, Indonesia.

Instruments

The crystallization process used an overhead stirrer (IKA Eurostar 20 digital). SEM (JEOL JSM-6510LV) analyzed particle morphology. FTIR (Bruker Alpha II) and DSC (Mettler Toledo DSC 1) characterized chemical and thermal properties. PXRD (PANalytical X'Pert PRO) determined crystallinity. A USP type II apparatus (Erweka DT 720) was used for dissolution. Micromeritic properties were evaluated using standard volumetric tools (Merck KGaA, Darmstadt, Germany) to assess flow and compressibility.

Solvent Selection Criteria

The selection of solvents for the spherical crystallization process adhered to principles critical for agglomerate formation. Methanol was used as the good solvent for its strong solvating power for atorvastatin and its volatility, which supports efficient crystallization upon diffusion into the poor solvent (Chen et al., 2020). Water, chosen as the poor solvent, enabled controlled precipitation of the drug by decreasing its solubility and promoting supersaturation upon contact with the methanolic solution (Lee et al., 2022). Dichloromethane was used as the bridging liquid to promote particle aggregation and droplet formation during crystallization. Its low solubility for atorvastatin and intermediate miscibility with methanol and water make it ideal for supporting bridge formation between crystallizing particles (Hu et al., 2023; Tahara et al., 2018).

Spherical Crystallization Procedure

Spherical crystallization was performed using the quasi-emulsion solvent diffusion (QESD) method. Atorvastatin calcium (500 mg) was dissolved in 10 mL of methanol to form the drug solution. Separately, 2 mL of dichloromethane was added dropwise under stirring to serve as the bridging phase. The resulting mixture was slowly poured into 100 mL of distilled water containing 0.25% w/v HPMC E50, maintained at 25 ± 2°C, and stirred at 500 rpm using a mechanical stirrer. Stirring was continued for 2 hours to allow complete solvent diffusion and the formation of spherical agglomerates. Crystals were filtered, washed with water, and dried at room temperature for 24 hours (Tahara et al., 2018).

Characterization with Scanning Electron Microscopy (SEM)

The morphology and surface texture of the agglomerates were analyzed using SEM. Samples were coated with gold before being scanned at an accelerating voltage of 15 kV. The spherical nature, particle size uniformity, and surface smoothness of the agglomerates were evaluated to confirm successful crystallization and the impact of solvent ratios and polymer inclusion on particle structure (Chen et al., 2019a).

Characterization with Fourier-Transform Infrared Spectroscopy (FTIR)

FTIR was employed to detect any potential chemical interactions between atorvastatin calcium and HPMC E50 or solvent residues. Spectra were recorded in the range of 4000–400 cm^{-1} using the potassium bromide (KBr) pellet method. Characteristic functional groups of atorvastatin were identified and compared with spectra from spherical agglomerates to assess compatibility and chemical stability (Wu et al., 2015).

Characterization with Differential Scanning Calorimetry (DSC)

DSC analysis was performed to evaluate thermal transitions and assess potential polymorphic changes during spherical crystallization. Approximately 5 mg of the sample was sealed in an aluminium pan and scanned from 30°C to 300°C at a rate of 10°C/min. The melting point and enthalpy changes of pure atorvastatin and spherical agglomerates were compared to determine any alterations in crystallinity (Chen et al., 2019b).

Characterization with Powder X-ray Diffraction (PXRD)

PXRD was utilized to examine the crystallinity and phase purity of the spherical agglomerates. Diffraction patterns were recorded over a 2θ range of 5° to 40° with a step size of 0.02°. The intensity and sharpness of peaks were compared with those of raw atorvastatin to identify changes in crystallinity resulting from the QESD process. Reduction in peak intensity was used as an indicator of partial amorphization or polymorphic transition (Peña et al., 2019).

Evaluation of Micromeritic Properties

Micromeritic characteristics, including angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio, were measured to evaluate flowability and compressibility. The angle of repose was determined using the fixed-funnel method, and bulk and tapped densities were measured with a graduated cylinder after gentle tapping. These parameters were used to calculate Carr's index and Hausner ratio. Improved values for these indicators signified enhanced powder handling properties, confirming the suitability of the agglomerates for direct compression (Peña et al., 2019).

Dissolution Testing

Dissolution studies were conducted using a USP Type II (paddle) apparatus with 900 mL of phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C and a paddle rotation speed of 50 rpm. Samples equivalent to 10 mg of atorvastatin were placed in the dissolution media, and aliquots were withdrawn at predefined time intervals (5, 10, 15, 30, 45, and 60 minutes). The samples were filtered, and drug concentrations were determined using UV-visible spectrophotometry at 246 nm. Dissolution profiles of the spherical agglomerates were compared to those of raw atorvastatin to evaluate the enhancement in solubility and release rate (Chen et al., 2019b; Wu et al., 2015).

RESULTS AND DISCUSSION

Physicochemical Characterization

To evaluate the potential impact of the crystallization process on the physicochemical properties of atorvastatin calcium, FTIR, DSC, and PXRD analyses were conducted to assess chemical integrity, thermal behavior, and crystalline structure, respectively. These methods are widely used in pharmaceutical studies to confirm drug–excipient compatibility, detect structural changes, and assess crystallinity (Canbay & Doğantürk, 2018; Singh et al., 2024).

The FTIR spectra of pure atorvastatin and its spherical agglomerates (Figure 2: FTIR.png) showed no significant shift in characteristic peaks, indicating the absence of chemical interactions between atorvastatin and the stabilizer HPMC E50. Key functional group peaks—including those attributed to hydroxyl (O–H), carbonyl (C=O), and aromatic C–H stretching—remained unaltered in the agglomerated form. The close spectral overlap between the two samples suggests that the crystallization process preserved the molecular structure of atorvastatin, confirming compatibility and physical stability (Canbay & Doğantürk, 2018; Singh et al., 2024).

The DSC thermograms (Figure 1) further support the thermal and structural stability of atorvastatin following spherical crystallization. The pure drug exhibited a distinct endothermic peak near 159–162 °C, corresponding to its melting point. At the same time, the spherical agglomerates showed a slightly broadened and lower-intensity endothermic event in the same region. This attenuation suggests a reduction in crystallinity, likely due to the recrystallization conditions and presence of HPMC (Ghosh et al., 2019; Salam et al., 2020). However, the absence of new peaks or significant thermal transitions indicates that no polymorphic transformation or degradation occurred during processing.

PXRD analysis provided further insight into the crystalline structure of atorvastatin pre- and post-spherical crystallization (Figure 3: PXRD). The diffractogram of pure atorvastatin exhibited multiple sharp, intense peaks, indicating high crystallinity. In contrast, the PXRD pattern of spherical atorvastatin agglomerates displayed a noticeable reduction in peak intensity and slight broadening, indicating a decrease in crystallinity and possible partial amorphization. These structural modifications are often correlated with enhanced solubility and dissolution properties, as also supported in related studies (Islam et al., 2021; Markeev et al., 2023).

Together, FTIR, DSC, and PXRD data confirm that the spherical crystallization process preserved the chemical integrity of atorvastatin while reducing its crystallinity—changes that may contribute to improved pharmaceutical performance in terms of solubility and compressibility. These findings are consistent with reports that particle engineering can enhance functionality without compromising stability (Islam et al., 2021).

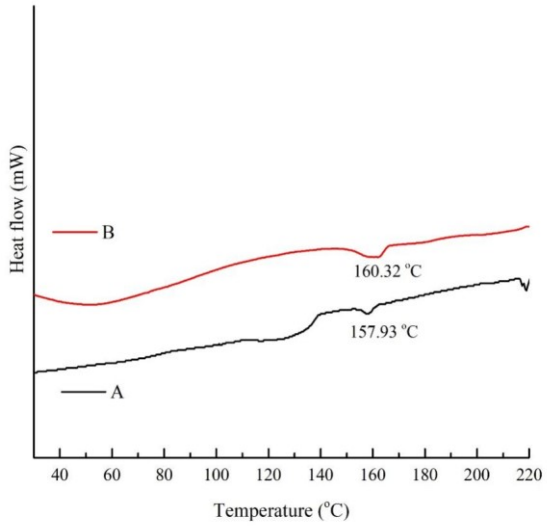

Figure 1. Differential Scanning Calorimetry (DSC) thermograms of pure atorvastatin (A) and spherical atorvastatin agglomerates (B).

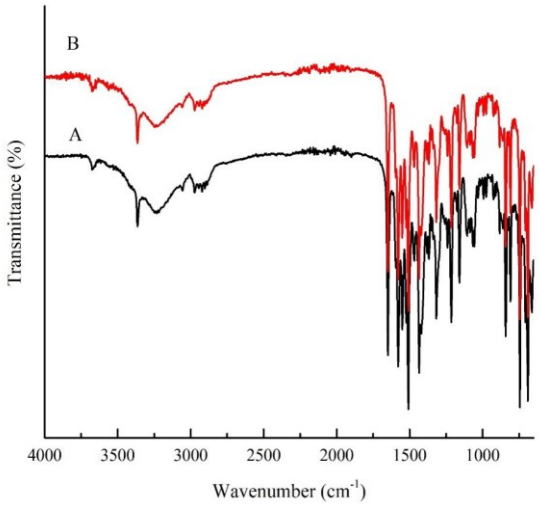

Figure 2. FTIR spectra comparing pure atorvastatin (A) and spherical atorvastatin agglomerates (B).

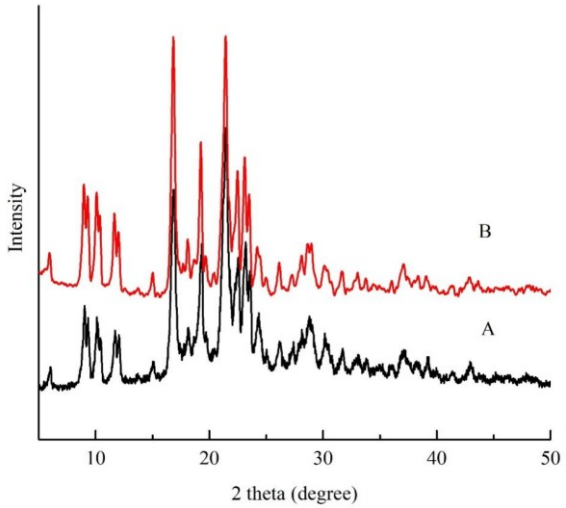

Figure 3. PXRD diffractograms of pure atorvastatin (A) and spherical atorvastatin agglomerates (B), showing reduced crystallinity post-crystallization.

Morphology and Micromeritic Properties

Spherical crystallization markedly altered the morphology and micromeritic properties of atorvastatin calcium. Figures 4 and 5, featuring scanning electron microscopy (SEM) images reveal a significant morphological transformation from irregular, rough-surfaced raw atorvastatin crystals to smooth, well-rounded spherical agglomerates during crystallization. This change aligns with previous reports that spherical crystallization enhances uniformity and reduces inter-particle friction, ultimately improving flowability (X. Wang et al., 2024; X. Zhang et al., 2020).

Micromeritic evaluation (Table 1) revealed substantial improvements in flow and packing behavior. The flow rate of spherical atorvastatin increased significantly from 0.92 g/s in the raw form to 5.8 g/s post-crystallization. The angle of repose decreased from 32.37° to 29.32°, indicating improved flow properties due to reduced interparticle cohesion. These findings are consistent with Gyulai et al. (2017) and Espitalier et al. (1997), who emphasized that spherical morphology supports efficient powder handling.

Bulk density rose from 0.1687 g/mL to 0.3436 g/mL, and tapped density improved from 0.2184 g/mL to 0.4095 g/mL, showing better packing efficiency due to the regular shape and surface of the agglomerates. True density also increased markedly. These changes led to a reduction in compressibility index from 23.12% to 16.03% and a Hausner ratio drop from 1.30 to 1.18, confirming enhanced compressibility and reduced compressive resistance, consistent with the findings of (Chatterjee et al., 2017; X. Wang et al., 2024).

The improved morphological and micromeritic properties observed in spherical agglomerates of atorvastatin support their suitability for direct-compression tablet manufacturing. These enhancements align with literature highlighting that spherical particles improve flow, reduce punch sticking, and allow for more consistent dosing in high-speed manufacturing environments (Mishra et al., 2020; Yazdanpanah et al., 2017).

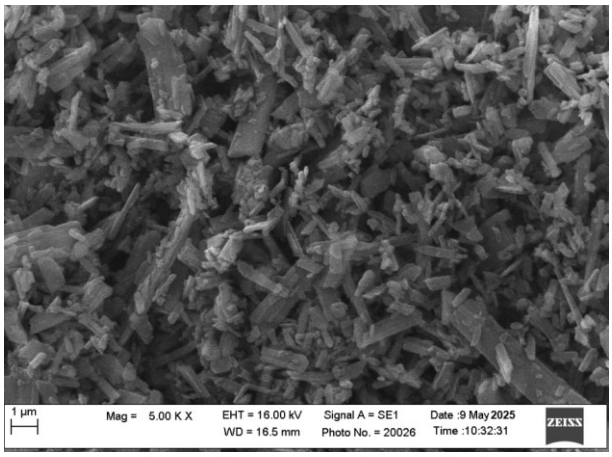

Figure 4. SEM image of raw atorvastatin crystals showing irregular morphology (Magnification: 5000x).

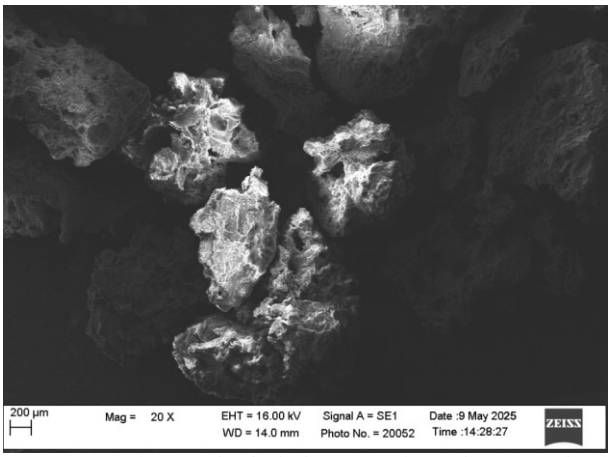

Figure 5. SEM image of spherical atorvastatin agglomerates showing smooth, round surfaces (Magnification: 20x).

Table 1. Micromeritic properties of raw and spherical atorvastatin powders (n = 3).

Parameter	Raw Atorvastatin	Spherical Atorvastatin
Flow Rate (g/s)	0.92 ± 0.12	5.80 ± 0.72
Angle of Repose (°)	32.37 ± 3.82	29.32 ± 0.50
Bulk Density (g/mL)	0.17 ± 0.001	0.34 ± 0.01
Tapped Density (g/mL)	0.22 ± 0.01	0.41 ± 0.02
True Density (g/mL)	0.62 ± 0.23	1.21 ± 0.02
Compressibility (%)	23.12 ± 2.17	16.03 ± 2.36
Hausner Ratio	1.30 ± 0.04	1.18 ± 0.03
Compressibility Index (%)	23.11 ± 2.18	16.03 ± 2.35

Dissolution Testing

The dissolution behavior of atorvastatin calcium significantly improved following spherical crystallization, as demonstrated by the dissolution profile shown in Figure 6. At every time point observed, spherical atorvastatin exhibited a markedly higher percentage of drug release compared to raw atorvastatin. At 5 minutes, the spherical agglomerates released 42.65% of the drug, while the raw form released only 8.12%. This trend was observed across all measured intervals, with spherical atorvastatin achieving 81.85% dissolution at 30 minutes, compared with 51.85% for the raw material.

These enhancements can be attributed to the increased wettability and surface area of the spherical agglomerates. The spherical morphology facilitates improved solvent penetration and more efficient interaction between the drug particles and the dissolution medium, leading to faster drug release. This finding is consistent with the literature, where enhanced dissolution performance has been reported for BCS Class II drugs processed through spherical crystallization due to reduced crystallinity and better powder dispersion (Indra et al., 2022)

Moreover, the presence of HPMC E50 during crystallization likely contributed to the improved dissolution profile. As a hydrophilic polymer, HPMC forms a gel-like layer around the drug particles in the dissolution medium, enhancing solvent interaction and maintaining drug supersaturation (Kwon et al., 2019; Zarmpi et al., 2020). The reduction in crystallinity, as indicated by DSC and PXRD, further supports the improved solubility and dissolution behavior.

Overall, the combination of spherical crystallization and polymer incorporation significantly enhanced the dissolution rate of atorvastatin, indicating a promising strategy for improving the bioavailability of poorly soluble drugs.

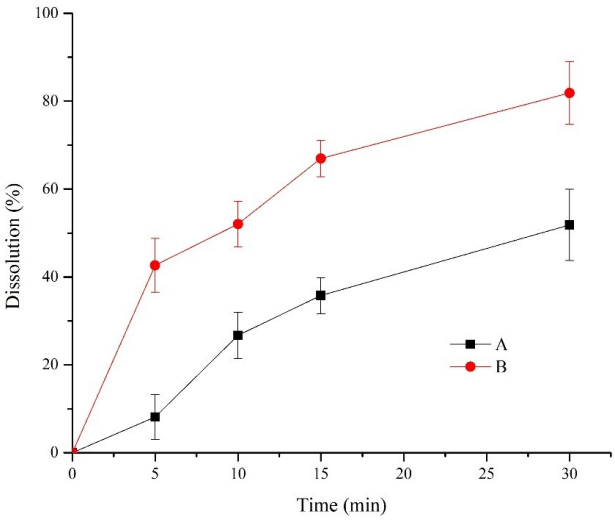

Figure 6. Dissolution profiles of raw (A) and spherical atorvastatin (B) in phosphate buffer (pH 6.8).

CONCLUSIONS

This study demonstrates that spherical crystallization using a quasi-emulsion solvent diffusion method in the presence of HPMC E50 significantly improves the pharmaceutical performance of atorvastatin calcium. The transformation of raw, irregular crystals into well-formed spherical agglomerates resulted in enhanced micromeritic properties, including increased flowability, higher bulk and tapped density, and improved compressibility. These characteristics are essential for the manufacture of direct-compression tablets and indicate the potential for simplified and efficient processing.

The physicochemical characterization confirmed that the crystallization process did not induce any chemical interaction between the drug and excipients. At the same time, thermal and X-ray analyses indicated a partial reduction in crystallinity. This change, coupled with the morphological modification, contributed directly to the observed enhancement in dissolution behavior. Spherical atorvastatin agglomerates exhibited a markedly higher dissolution rate than the raw material, supporting their potential to increase bioavailability in oral dosage forms.

These findings contribute to the growing body of evidence supporting particle engineering as an effective strategy to overcome formulation challenges associated

with BCS Class II drugs. The integration of HPMC as a stabilizing polymer further enhances functionality by maintaining supersaturation and promoting solubility. Future studies could explore scale-up parameters, in vivo bioavailability correlations, and applications of this approach to other poorly soluble compounds.

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Authors' Contributions: Indra and Ria Marliana Tika designed the study. Ria Marliana Tika carried out the laboratory work. Indra and Winda Trisna Wulandari analyzed the data. Indra, Ria Marliana Tika, & Winda Trisna Wulandari wrote the manuscript. All authors read and approved the final version of the manuscript.

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