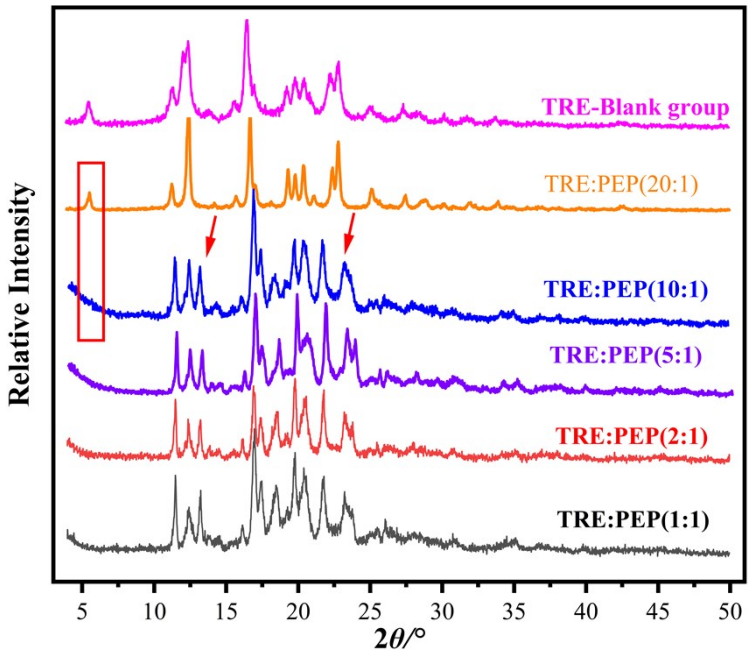

Fig. S1. PXRD patterns of trelagliptin crystal forms obtained by milling mixtures of TRE and PEP at different weight ratios.

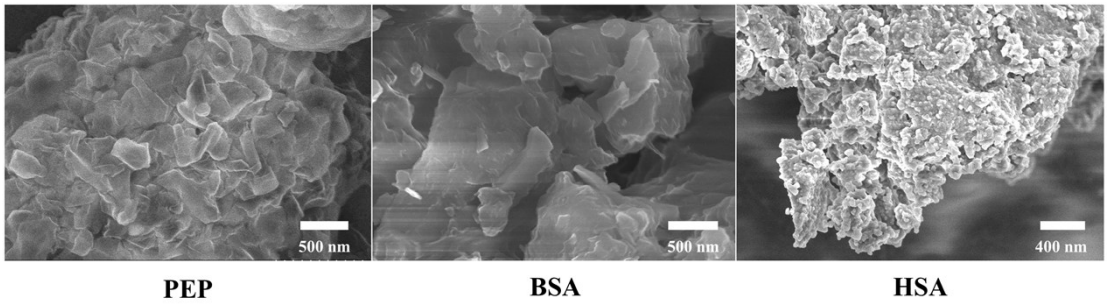

Fig. S2. SEM images of PEP, BSA, and HSA.

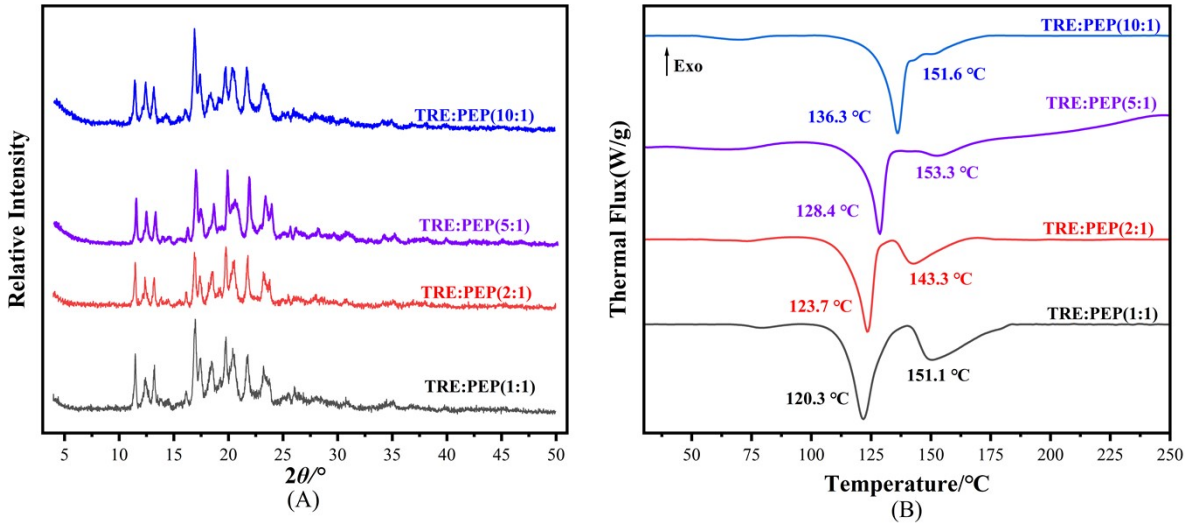

Fig. S3. (A) PXRD patterns and (B) DSC profiles of TRE-F obtained by milling mixtures of TRE and PEP at different weight ratios.

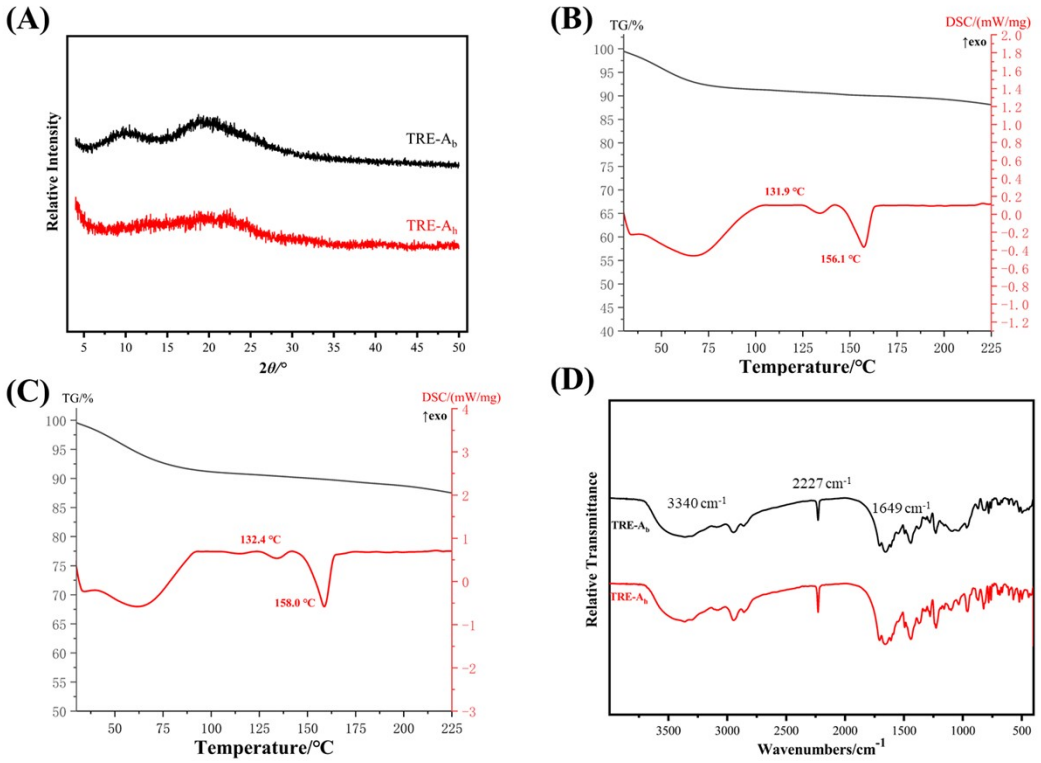

Fig. S4. Comparative characterization of TRE-Ab and TRE-Ah by (A) PXRD, (B, C) DSC and TGA, and (D) FT-IR, demonstrating the remarkable similarity between TRE-Ab and TRE-Ah. (The PXRD patterns of TRE-Ab and TRE-Ah display characteristic amorphous features, namely broad, diffuse scattering peaks extending across a wide angular range. Closer comparison reveals that the geometric profiles of the diffuse peaks are highly similar between TRE-Ab and TRE-Ah, with nearly identical peak positions and peak shape contours, indicating that the two forms share a comparable amorphous solid-state structure. DSC curves of TRE-Ab and TRE-Ah show that TRE-Ab exhibits two distinct endothermic events at 131.9°C and 156.1°C, whereas TRE-Ah displays similar endothermic events at 132.4°C and 158.0°C. Furthermore, the TGA curves of TRE-Ab and TRE-Ah differ only negligibly, suggesting that the amorphous forms obtained via HSA- and BSA-mediated mechanochemistry yield comparable thermal profiles. FT-IR spectra of both TRE-Ab and TRE-Ah exhibit a prominent broadened absorption envelope centered at 3440 cm^{-1}, reflecting protein-mediated reconstruction of the crystalline hydrogen-bonding network and associated spectral perturbations. In addition, both forms display highly similar spectral features at 2227 cm^{-1}, corresponding to the characteristic C≡N stretching absorption, as well as comparable amide band shifts at 1649 cm^{-1}. The close resemblance in peak profiles between TRE-Ab and TRE-Ah suggests a consistent intermolecular interaction environment, further demonstrating the remarkable similarity between the two amorphous forms.)

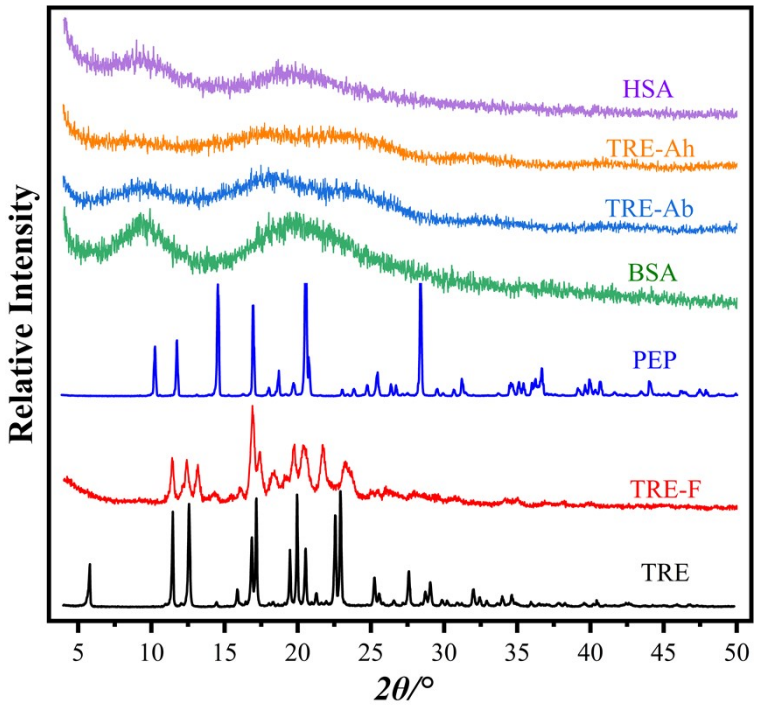

Fig. S5. Comparison of PXRD patterns of three proteins, three newly discovered solid forms of trelagliptin (TRE-F, TRE-Ab, and TRE-Ah), and the original TRE.

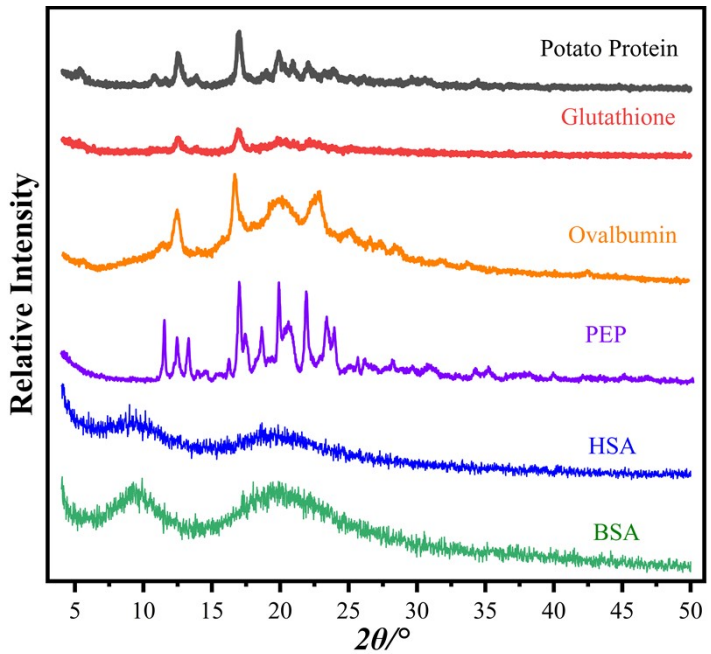

Fig. S6. Comparison of PXRD patterns of trelagliptin solid forms obtained by different protein-mediated under milling (PXRD patterns of trelagliptin solid forms induced by ovalbumin, potato protein, and glutathione under milling are similar to those of the original crystal form TRE milled without protein. Among the proteins tested, only BSA, HSA, and PEP-which exhibit strong interactions with the drug-successfully induced the transition to produce new crystal forms).