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<AT>Analysis of Low Active-Pharmaceutical-Ingredient Signal Drugs Based on Thin Layer Chromatography and Surface-Enhanced Raman Spectroscopy

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<ABS-Head><ABS-HEAD>Graphical abstract
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<ABS-HEAD>Highlights► 1 Low Active-pharmaceutical-ingredient Signal Drugs (LASIDs) was firstly defined. ► 2A tailored solution to the analytical problem of these LASIDs was proposed. ► 3 The solution was detailed, effective in detection of the LASIDs with high accuracy. ► 4 TLC-SERS was successfully developed and superior to Raman mapping and HPLC.
<ABS-HEAD>Abstract
<ABS-P>Active pharmaceutical ingredients (API) embedded in the excipients of the formula can usually be unravelled by normal Raman spectroscopy (NRS). However, more and more drugs with low API content and/or low Raman scattering coefficient were insensitive to NRS analysis, which was for the first time defined as Low API-Signal Drugs (LASIDs) in this paper. The NRS spectra of these LASIDs were similar to their dominant excipients' profiles, such as lactose, starch, microcrystalline cellulose (MCC), etc., and were classified into three types as such. 21 out of 100 kinds of drugs were screened as LASIDs and characterized further by Raman microscopic mapping. Accordingly, we proposed a tailored solution to the qualitation and quantitation problem of these LASIDs, using surface-enhanced Raman spectroscopic (SERS) detection on the thin layer chromatographic (TLC) plate both *in situ* and after-separation. Experimental conditions and parameters including TLC support matrix, SERS substrate, detection mode, similarity threshold, internal standard, etc., were optimized. All LASIDs were satisfactorily identified and the quantitation results agreed well with those of high performance liquid chromatography (HPLC). For some structural analogues of LASIDs, although they presented highly similar SERS spectra and were tough to distinguish even with Raman microscopic mapping, they could be successfully discriminated from each other by coupling SERS (with portable Raman