HPTLC as a problem solving technique in pharmaceutical analysis

Clare McKinlay - GSK, Medicines Research Centre, Stevenage

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Outline

- Historical use of TLC in pharmaceutical R&D
- Current situation – How HPTLC is still an essential part of the analysts toolkit
- Examples of successful applications
- What the future holds….

Past

Present

Future

Past

- Method of choice for analysis of pharmaceuticals in many USP monographs and in routine use up to 70’s/80’s
- Basic compendia methods are simple, rapid and robust
- Used by organic synthetic chemists to check reactions and is seen as the window to the reaction
- Before HPLC/GC instrumentation was widely utilised TLC was the main method for detection of process impurities in API

Present

- HPLC / GC, with their various modes of detection, are the techniques of choice for routine analysis
- TLC still used by synthetic chemists to monitor reactions
- With advances in instrumentation HPTLC is having a resurgence in popularity as a problem solving technique, exploiting the following strong features:-
  - Ability to “see” everything on the plate
  - Non destructive analysis / ease of isolation for structural elucidation
  - Wide variety of detection techniques for visualisation of non-chromophoric compounds
  - Parallel analysis allowing quick visual comparisons

Project examples – # 1

Investigation of a mass imbalance issue in a NCE (new chemical entity)

- Situation
  - Mass imbalance was observed in a stressed drug product sample
  - Various other chromatographic including HPLC DAD and spectroscopic techniques (including NMR) were investigated to find source of mass imbalance with no success
- HPTLC method and results

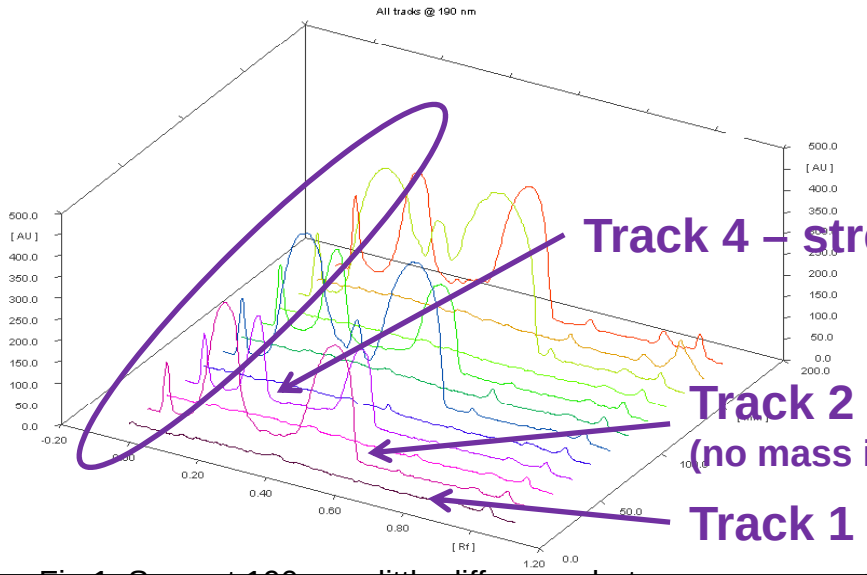

Fig 1. Scan at 190nm – little difference between control and degraded sample with mass imbalance

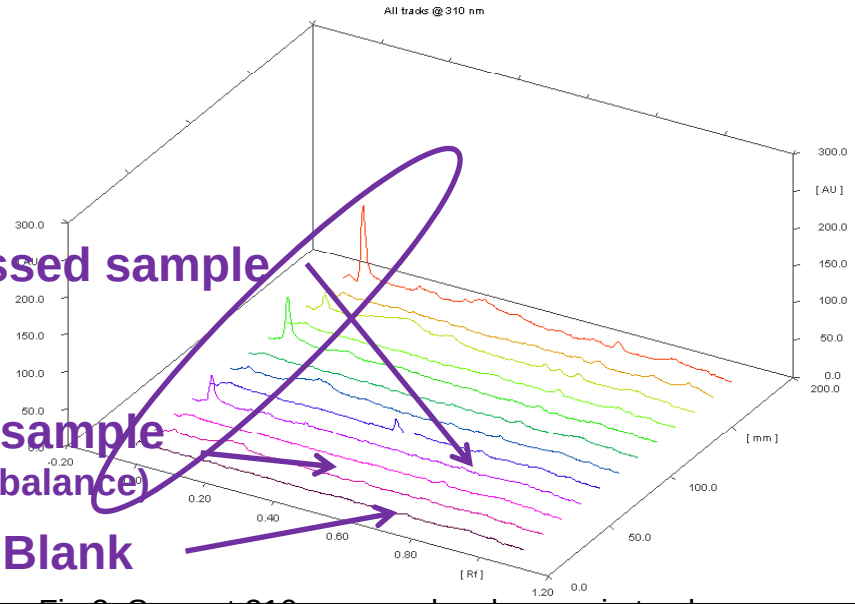

Fig 2. Scan at 310nm – peak only seen in tracks of degraded sample with mass imbalance

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Project examples – # 1

Investigation of a mass imbalance issue in a NCE (new chemical entity)

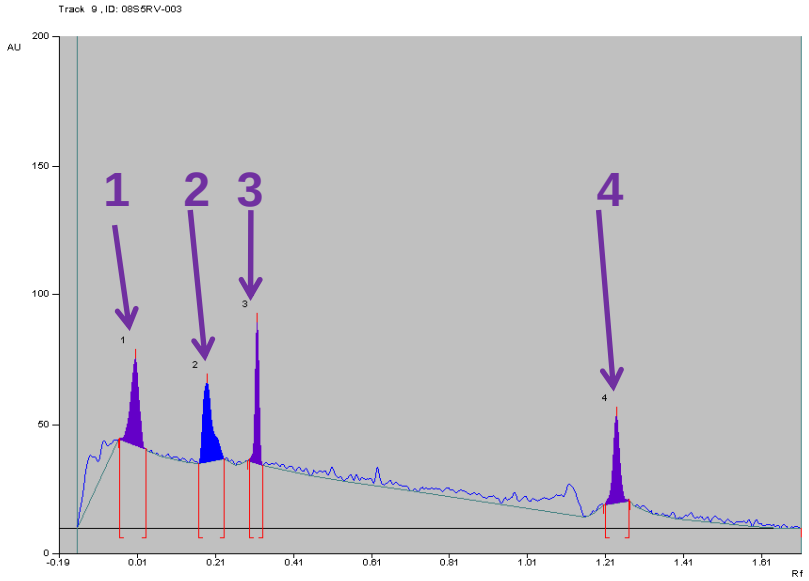
- Outcome
  - Results from analysis of degraded samples supported the assay method by showing that there was a impurity component present in the stressed sample that was not detected on the RP-HPLC-UV method.
  - The HPTLC method was used to analyse formal stability batches to check for the presence of this new impurity.
  - Preparative HPTLC run and samples supplied for further structural elucidation experiments
  - Information provided project team with greater understanding and assurance that the impurity was not being formed during formal stability studies

Project examples – # 2

Colour differences in API (Active pharmaceutical ingredient) derived from similar synthetic routes

- Situation
  - During process development for an API in development differences in colour were observed
  - Reversed phase and normal phase HPLC method investigated with no conclusive differences

- HPTLC methods and results
  - Method development screen conducted using radial development procedure to screen stationary phase / mobile phase combinations
  - Peaks1,3 and 4 observed in more coloured batches



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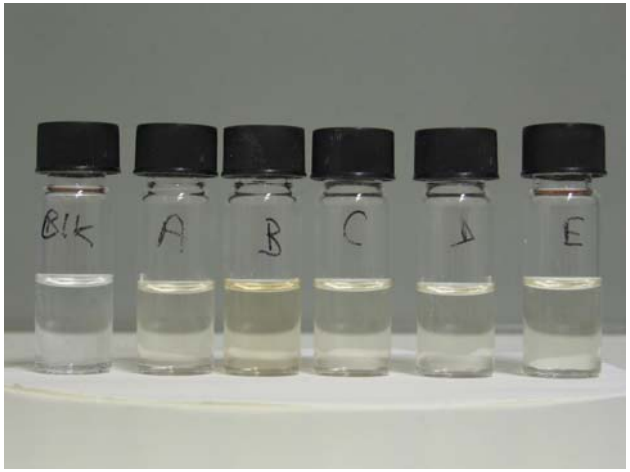
Project examples – # 2

Colour differences in API (Active pharmaceutical ingredient) derived from similar synthetic routes

- HPTLC methods and results (continued)
  - Instrument parameters optimised to give improved quantification (<3%RSD for low level imp)
- Outcome
  - Method used to screen batches to look for trends



Batches	Solid Colour	Area Peak 1 (Au)	Area Peak 3 (Au)	Area Peak 4 (Au)
A	Pale yellow	89	135	79
B	Brown	262	189	182
C	Pale y			
D	Pale y			
E	White	164	128	145

Anomaly in trend of results – solid appearance impacted by particle size

Project examples – # 3

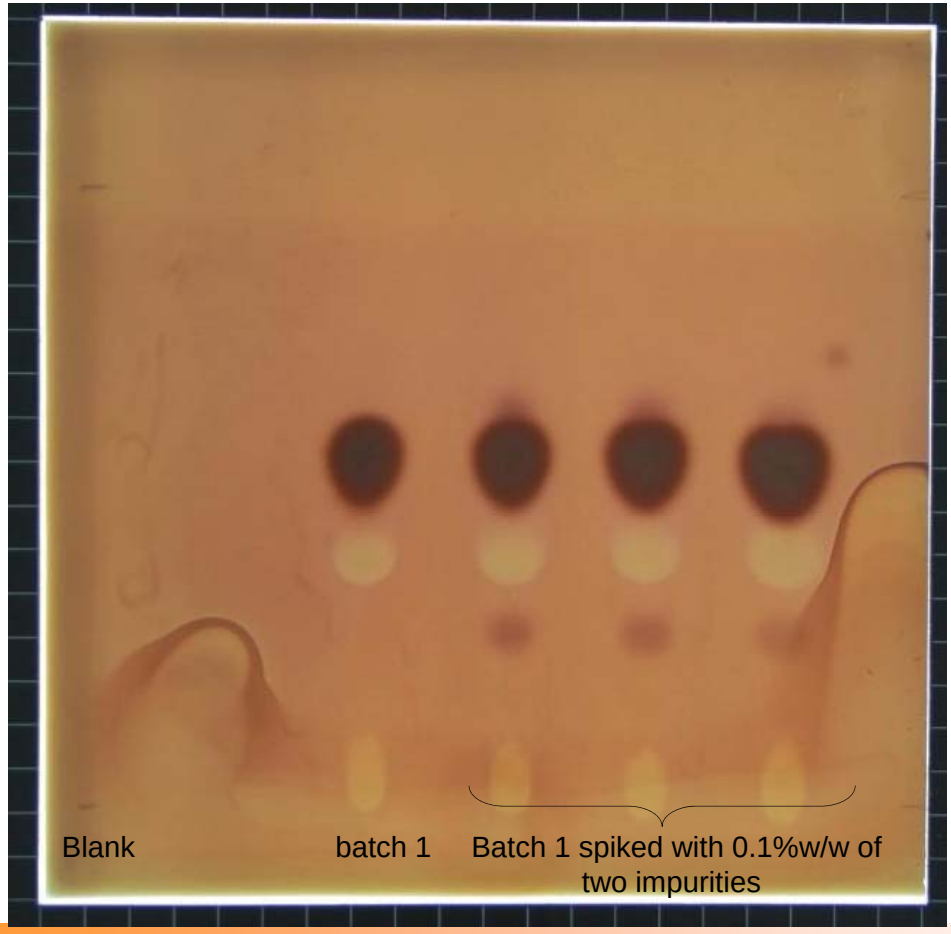
Development of an analytical method for non-chromophoric starting material

- Situation
  - A registered starting material in the synthesis of an API in development was analysed to determine impurity content by a GC method which was unreliable and unsuitable for transfer to manufacturing site
  - Several alternative methods proposed (HPLC derivatisation, Ion chromatography and TLC)
  - TLC was deemed the preferred method by the manufacturing site due to low method complexity
- TLC method and results
  - TLC method developed on silica plate with manual spotting, vertical development and visual detection using ninhydrin spray

Project examples – # 3

Development of an analytical method for non-chromophoric starting material

- TLC method and results



- Outcome
  - Suitable method developed to control two impurities in starting material to 0.1%w/w
  - Method validated to a suitable standard
  - Method transferred to manufacturing site and used routinely to analyse materials for commercial product

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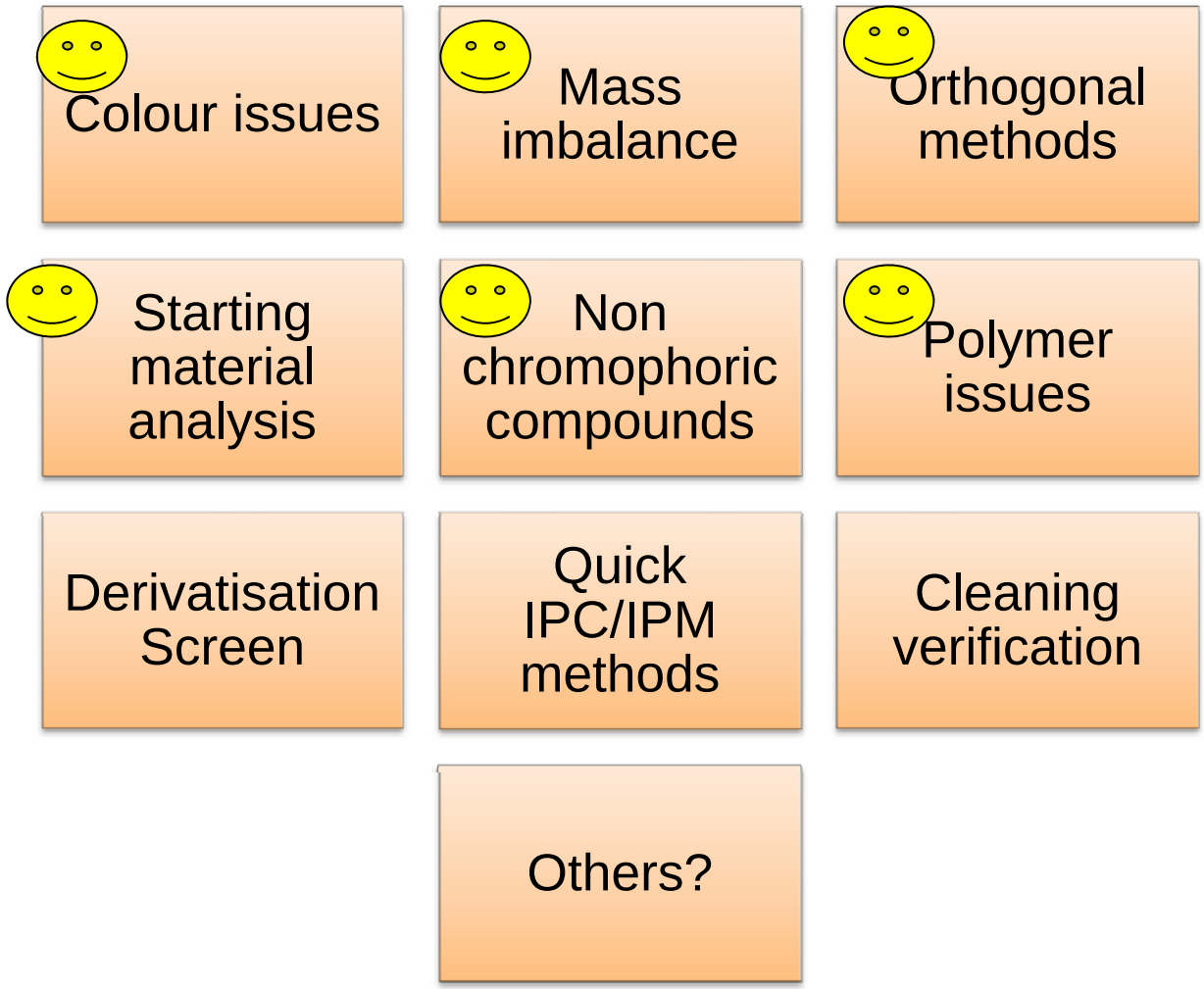
Future


Colour issues
Mass imbalance
Orthogonal methods
Starting material analysis
Non chromophoric compounds
Polymer issues
Derivatisation Screen
Quick IPC/IPM methods
Cleaning verification
Others?

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