USES OF CAPILLARY ELECTROPHORESIS FOR PHARMACEUTICAL QUALITY CONTROL IN JAPAN

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CE IN JAPANESE PHARMACOPOEIA

- Capillary electrophoresis procedures are described in General Information of JP (Japanese Pharmacopoeia).

- The pharmacopoeial texts can now be used interchangeably in ICH regions as the result of the Q4B process.
CE in Japanese Pharmacopoeia

- General principles
- Apparatus
  - 1. Capillary Zone Electrophoresis
  - 2. Capillary Gel Electrophoresis
  - 3. Capillary Isoelectric Focusing
  - 4. Micellar Electrokinetic Chromatography
THE USE OF CAPILLARY ELECTROPHORESIS IN JAPAN

- Survey: how capillary electrophoresis is used for pharmaceutical quality control in pharmaceutical companies in Japan

- Members of The Japan Pharmaceutical Manufacturers Association (JPMA)

- 21 Companies, 32 respondents
THE USE OF CAPILLARY ELECTROPHORESIS IN JAPAN

**Target: Area**

- Quality control: 41%
- Formulation development: 31%
- Process development of drug substances: 3%
- Manufacturing: 12%
- Other: 13%

**Scale of business**

- ≥ 30,000: 10%
- < 30,000: 14%
- < 10,000: 29%
- < 5,000: 19%
- < 2,000: 14%
- < 1,000: 9%
- < 200: 5%
- < 200: 5%
THE USE OF CAPILLARY ELECTROPHORESIS IN JAPAN

Status of use

- ≥ 30,000: % in use, % will be introduced, % not in use
- < 30,000: % in use, % will be introduced, % not in use
- < 10,000: % in use, % will be introduced, % not in use
- < 5,000: % in use, % will be introduced, % not in use
- < 2,000: % in use, % will be introduced, % not in use
- < 1,000: % in use, % will be introduced, % not in use
- < 200: % in use, % will be introduced, % not in use

(%)
e.g.) Physicochemical properties of drug substances, specification, quality test (drug substances, drug products, excipients), stability test, monitoring for manufacturing method, shipping test
EXAMPLE:
GLYCOSYLATION ANALYSIS OF IgG

PA800
eCAP PVA type Coated Capillary
Fluorescent labelled with APTS (8-aminopyrene-1,3,6-trisulfonate)

G0
G1A
G1B
G2

Time (min)
Q. Has CE become part of the specification and test method?

- Yes: 62%
- No: 24%
- Under consideration: 14%

E.g.:
- Purity test (CE-SDS, c-IEF, glycosylation mapping)
- Identification test
- Process control of drug substances
Advantages

- The variety of separation modes in the method.
- Quantitative performance, sensitivity, repeatability, automatization, short run time—compared to slab gel electrophoresis
- Small sample volumes, small effluent, characteristics of separation mode (e.g. ion analysis, charged compounds, highly polar compounds) -compared to LC
- The same software as for LC and GC
- Simultaneous analysis of various components
ADVANTAGES AND DISADVANTAGES OF CE IN DRUG DEVELOPMENT

Disadvantages

- Not yet in common use, High cost
- Not repeatable (injection volume, eluent time, response, quantification), Difficulties in fractionation and low sensitivity –compared to LC
- Instability in performance (unexpected trouble, clogging of the capillary tube, difficulty in system conditioning)
- Difficulty in the setting of analytical conditions
- Difficulty in peak characterization
- Discrepancy of analytical results between different companies’ instruments
- Matrix effect
The use of microchip electrophoresis in Japan

Status of use

- **Yes**: 23%
- **Under consideration**: 3%
- **No**: 74%

**Other (e.g. physicochemical properties)**: 4

**Manufacturing**: 0

**Quality control**: 1

**Formulation development**: 3

**Process development of drug substances**: 12

- **CE-SDS**
- **Glycosylation mapping**
GENERAL COMMENTS FROM USERS

- CE will become a more important method if it is applied to more chemical synthesis drugs.
- Great skill is required to get data with good repeatability.
REQUESTS TO MAKERS FROM USERS

- Devices to connect CE and MS
- Standardization of instrument specification between CE makers.
- Improvements in injection repeatability, automation of analytical optimization, and miniaturization of equipment
- Improvement of sudden instability in results
- Improvement of difficulties in injecting samples to equipment
- These improvements are necessary to enable an effective system suitability test.
REQUESTS TO REGULATORS FROM USERS

- Standardization of method validation in purity test of therapeutic antibodies
  - e.g.) - Accuracy of response factor for fluorescently-labeled antibodies
    - Robustness

- Standardization of injection method and washing method

- Standardization of method of calculating isoelectric point
CONCLUSION

- CE is an analytical method with many advantages such as quantitative performance, sensitivity, and short run time.
- However, there are some difficulties in the setting of analytical conditions, and peak characterization.
- By improving these difficulties, CE can be in more common use as methods for characterization, quality controls, and specification.
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Thank you for your attention!