Analytical control of 5-fluorouracil diffusers, finally possible?

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Introduction :

5-Fluorouracil (5FU) is one of the most prescribed anticancer drugs, mainly in the treatment of colorectal cancer. Its administration scheme consists of a bolus combined with administration over several days using a diffuser.

The preparation of the diffuser is done into 2 steps :

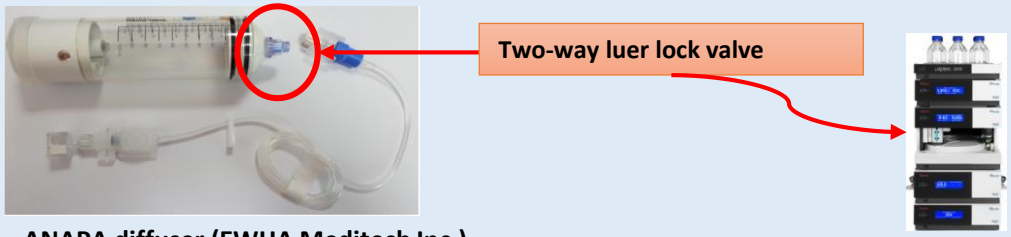
- injection of the solvent (NaCl) for purging of the extender
- the filling of the required volume of 5FU

In our unit, this preparation is done either for a specific patient or most of the time by batches.

Aim : To evaluate the feasibility of analytical control.

2 types of diffusers :

- **Elastomeric** ➔ Non-drawable
- **Non-elastomeric:** Flow rate regulated by CO_2 ➔ **Drawable**
  - Presence of a two-way valve ➔ analytical control



ANAPA diffuser (EWHA Meditech Inc.)

Material and Methods :

- **Validation of the analytical method** according to ICH Q2R1 (linearity, accuracy, repeatability, reproducibility).
  - A continuous flow UV-DAD HPLC (FIA) method using a Dionex® Ultimate 3000 chain and Chromeleon® 7.0 software was developed.
- **Preparation of 18 2-day diffusers**
  - Calculation of the absolute relative error (RE)
  - Calculation of the percentage of second samples
  - The acceptance limits : ± 15%

❖ **A double visual check for all diffusers**

Results :

❖ FIA conditions : **100% water**, **flow-rate = 1,5 ml/min**, **injection volume=1 µl**, **λ=269nm**

❖ Method :

- **Linear** : **R^2 = 0,998**
- **Fair** : **TR =99,4%** [96%; 103.2%]
- **Repeatable** : **CV = 1,0%**
- **Reproducible** : **CV = 1,4%**

❖ **18 diffusers prepared between 3400 and 5000 mg.**

Relative errors	Diffusers percentages
< 10%	61% (n=11)
Between 10% et 15%	28% (n=5)
> 15%	**11%** (n=2)

2nd samples after homogenization
- **n°1** : 29% then **3%**
- **n°2** : 35% then **0,3%**

100 % of diffusers released

Conclusion

- **Quality control is a major asset for this medical device.**
- **A re-sampling rate of 11% is to be compared to our standard rate of 1,3%. Harmonisation of the sampling method (3 syringe back and forth).**
- **For a referencing**, other criteria are to be studied: **flow-rate regularity, ergonomics of filling, secure sampling, and patient's comfort (weight, size).**
- **Other methods been studied but require specific material (Raman) or a new process of compounding (mother bag compounding and distribution).**