In Vitro—In Vivo Correlation: Modified Release Tablets Containing Furosemide Complexed with Hydroxypropyl-ß-cyclodextrin

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**Purpose**
Furosemide (FR) is a diuretic used as antihypertensive. However, this drug doesn’t have definition according to Biopharmaceutical classification system (BCS), since it has low solubility and difficult permeability predicting. Cyclodextrins (CD) improves BCS characteristics as solubility and/or permeability, so it was chosen to change FR biopharmaceutical characteristics. An in vitro – in vivo correlation (IVIVC) is defined by FDA as a predictive mathematical model describing the relationship between an in vitro property of a dosage form and an in vivo response. Therefore, the study aim was to obtained a IVIVC for modified release solid dosage forms containing furosemide complexed with hydroxypropyl-ß-cyclodextrin (HP-ß-CD) from dissolution and bioavailability assays.

**Methods**
Hydroxypropylmethylcelulose (HPMC) matrix tablets with FR (50mg) and HP-ß-CD were formulated and submitted to dissolution assay using apparatus IV for 8 hours in accordance with pharmacopoeial specifications, with pH gradient (pH1.2, 1 h; pH4.5, 1h; pH 6.8, 6h) and flow: 8mL/min. The selected formulations (A1, A2a, A3) and the intravascular formulation Furosemida Teuto IV® (20mg FR, reference) were used in the bioavailability assay, which was carried out under ethical guidelines. 12 healthy volunteers participated to the assay which was conducted for 8 hours and with a 7-day wash out. The correlation was obtained by plotting absorption fraction data, obtained from FR plasmatic curves through a deconvolution technique, against dissolution fraction data.

**Results**
The results showed that the HPMC concentration increase produces a decrease of the drug dissolution rate. In dissolution assay, formulations A1, A2a and A3 represent the following cumulative dissolution percentages after 8 hours, 42.60%, 55.97% and 86.70% (Figure1), and the dissolution efficiency (%) as follows: 26.40%, 43.27% and 73.85%. For bioavailability assay, the following results were obtained for formulations A1, A2a, A3 and IV, respectively: Cmax 0.6µg/mL, tmax 2.1h, AUC0-t 1.5µg.h/mL; Cmax 1.2µg/mL, tmax 2.8h, AUC0-t 2.2µg.h/mL; Cmax 2.1µg/mL, tmax 1.6h, AUC0-t 3.0µg.h/mL; and Cmax 4.3µg/mL, tmax 0h, AUC0-t 4.1µg.h/mL (Figure2). There was a significant linear relationship between dissolution and absorption fraction considering the formulations ($r^2=0.9609$) (Figure3).

**Conclusion**
The absorption and the apparatus IV dissolution data had a determination coefficient of 0.9609 for linear correlation.

![Dissolution Aparato IV](image1)
![Mean Plasmatic curve](image2)
![In vitro - in vivo correlation - Aparato IV](image3)