7. Summary of work

The present thesis is generally divided into three parts:

Part 1: *in-vitro* study for determine aerodynamic characterizations and compare the efficacy of five different nebulizers and two types of connections during ACI.

Part 2: *in-vivo* study for determining the drug delivering efficacy of the tested devices to the lungs.

Part 3: *ex-vivo* study to identify the total emitted dose that a subject would have received by the tested devices.

Salbutamol is a potent short acting β2-agonist, recommended for first line management of asthma and COPD acute exacerbations. Nowadays, measurement of pulmonary drug deposition has gained a great importance in the context of drug development. The available methods used for this purpose are simulated *in-vitro* studies and *in-vivo* pharmacokinetic methods which can together reflect the amount of inhaled drug.

In-vitro studies include the determination of aerodynamic particle distribution are commonly used for quality control testing of inhaled products. While pharmacokinetic methods using either plasma or urine samples can predict the relative pulmonary drug delivery (the effective lung dose) and also the total systemic delivery.

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While in pharmacokinetic studies, urinary salbutamol concentration is measured 30 minutes after dose inhalation during the absorption lag time of swallowed drug portion so this measured concentration and the calculated amount would account for the drug fraction absorbed mainly from lungs and can be used as a meaningful measure of pulmonary deposition. (Hindle and Chrystyn 1992)

Hence the objectives were:

a) To determine the aerodynamic characterizations of emitted aerosol of salbutamol from inhalation devices (jet and vibrating mesh nebulizers) (Fine particle dose (FPD $\leq$ 5μm and FPD $\leq$ 3μm), Fine particle fraction (FPF $\leq$ 5μm and FPF $\leq$ 3μm), Mass median aerodynamic diameter (MMAD) and geometrical standard deviation (GSD)) using ACI (Anderson Cascade Impactor).

b) Comparing the efficacy of five different nebulizers and two types of connections using ACI.

c) To evaluate the effect of inhalation techniques on the lung and systemic bioavailability in healthy volunteer subjects following inhalation from different three jet devices.

d) To compare the *in-vivo* (linked to *ex-vivo*) fate of nebulized salbutamol from different three inhalation jet devices in healthy volunteer subjects.

In the *in-vitro* part of the study, the main focus was comparing aerodynamic particle size distribution of the emitted-dose of 2 ml salbutamol solution at a flow rate of 15 L/min^{-1} using Anderson Cascade Impactor (ACI) through five different nebulizers using two different connections (holding chamber (Circulaire) and standard T-piece).The five devices were three jet nebulizers (VixOne, NebuTech Breath-Enhanced and En full Kit) and two vibrating mesh nebulizers(Aerogen Solo (SOLO) and Aerogen pro (PRO)).

The results of our *in-vitro* study demonstrated that T-piece with SOLO and PRO shows the highest significance in TDPS, CCD and FPD <5 Mic than other devices ($p<0.001$). T-piece with NebuTech has the highest significance in FPD <3 Mic and FPF <5 Mic% ($p<0.001$) and the lowest significance in MMAD ($p<0.05$) than the other devices. Circulaire with VixOne has significantly higher FPF <3 Mic% than and significantly lower MMAD than T-piece with VixOne ($p<0.05$) and ($p<0.001$), respectively.

In the *in-vivo* part of the study, three devices were selected to be tested in this part based on their encouraging *in-vitro* results: VixOne, NebuTech and En-full-Kit. Twelve subject (range 25-40 years, mean age of 23 years) healthy volunteer subjects. Each subject inhales nebulized-aerosol of 1 ml of salbutamol respirable solution (Farcolin respiratory solution

containing a nominal dose of 5000 $\mu g.ml^{-1}$ salbutamol through the three JNs using normal tidal-breathing. Two urine samples are taken from each patient: the first one is the urine voided 30 minute from dose inhalation and the other one is the urine pooled to 24 hour after dose inhalation.

The results of our *in-vivo* study demonstrated that Using T- piece with NebuTech and Kit result in USAL 0.5 significantly greater by about one fold or may be more than that delivered by VixOne and NebuTech using Circulaire ($p<0.001$).However, there is no any significance difference in USAL 24 between the three jet nebulizers by using T-piece or Circulaire.

Filters interposed between the mouthpiece and connections (holding-chamber system or the T-piece) trapped any drug likely to be inhaled. The amount of salbutamol deposited on the filter was assayed by high performance liquid chromatography in *ex-vivo* study.

The results of our *ex-vivo* study showed that T-piece with kit nebulizer results in higher SALF significance than T-piece with NebuTech or the Circulaire with Kit *($p<0.05$)*.