NEAR-ORIFICE SPRAY AND VALVE FLOW REGIME OF A PHARMACEUTICAL PRESSURISED METERED DOSE INHALER

H.K. Versteeg and G.K. Hargrave
h.k.versteeg@lboro.ac.uk , g.k.hargrave@lboro.ac.uk
Wolfson School of Mechanical and Manufacturing Engineering, Loughborough University, Loughborough, LE 11 3TU, UK

Abstract

We report the findings of two high-speed imaging studies to visualise the transient flow and primary atomisation process of a pharmaceutical pMDI: (i) external spray in the near-orifice region produced by a commercially available pMDI actuator package and (ii) flow in the expansion chamber and spray in the near-orifice region of a rectangular model of the commercial pMDI valve. The external visualisations revealed broadly similar spray characteristics for the commercial pMDI and the rectangular model. Imaging of the propellant flow inside the expansion chamber of the rectangular model showed the existence of an annular flow regime with a vapour core and an unsteady wall film consisting of foamy liquid. Simultaneous visualisations of internal flow and near-orifice spray allowed us to establish links between the flow regime in the expansion chamber and the nature of the external spray. Knowledge of the pre-atomisation mechanisms in two-orifice systems is important for improved control of the external spray characteristics and hence improved drug delivery efficiency of pharmaceutical pMDIs. Our results highlight the potential of optical diagnostics in the development of an improved account of the state of the flow inside a pMDI valve and its relationship with drop formation.

Introduction

In a pharmaceutical pressurised metered dose inhaler (pMDI) a mixture of propellant, excipients and drug is dispensed as suspension or solution by means of a two-orifice system. *External* spray characteristics in the far-field have been documented by Fletcher (1975), Clark (1991) and Dunbar (1996), the latter using Phase Doppler Anemometry (PDA). The results of this work along with temperature and pressure measurements by Fletcher (1975) and Clark (1991) suggest the following qualitative description of the processes *inside* a pMDI valve:

- Prior to actuation, a known amount of mixture is contained in the metering chamber of the pMDI. As the valve is depressed liquid propellant starts to flow through the valve orifice into the valve stem. Flash boiling of the liquid takes place in the metering chamber and a two-phase mixture enters the valve stem.
- Air, which initially fills the valve stem/expansion chamber, is quickly entrained by the incoming propellant two-phase mixture. The pressure in the valve stem/expansion chamber is lower than the metering chamber, but higher than atmospheric, so two-phase mixture is expelled through the actuator orifice.
- Here the final spray is produced before it enters the ambient atmosphere. Liquid ligaments embedded in the propellant vapour are torn apart by flow forces and small droplets are formed.
- The droplets move away from the actuator orifice and entrain surrounding air. Heat supplied by this entrained air causes further evaporation of droplets.
- Discharge continues until the pressure in the metering chamber and valve stem is equal to atmospheric.

Noting the downward deflection of the spray plume, Dunbar (1996, 1997[a,b]) proposed that this may be caused by the formation of asymmetric recirculation zones at the inlet corners of the actuator nozzle. He suggests that flash boiling is triggered here and, referring to work by Domnick and Durst, also describes a cyclic process of growth and collapse of these regions leading to spray pulsations with a frequency around 700Hz. Due to the absence of suitable instrumentation much of the above is based on circumstantial evidence. Fletcher (1975) and Dunbar (1996) both present small selections of high-speed photographs, but it is difficult to obtain a clear picture of flow conditions. In this paper we report the findings of flow visualisation studies of the transient flow and primary atomisation process of a pharmaceutical pMDI:

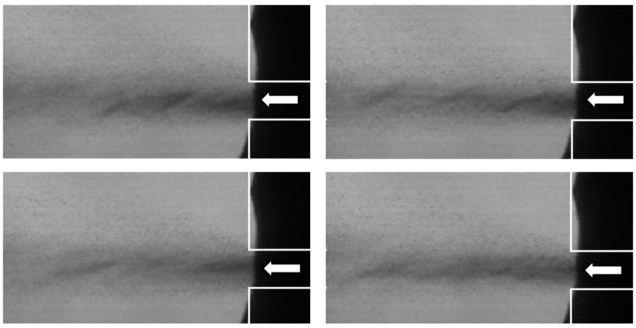
(i) High-speed imaging of the flow in the near-orifice region of a commercially available pMDI actuator package.
(ii) High-speed imaging of the flow in the expansion chamber and near-orifice region of a rectangular model of the commercial pMDI actuator package.

Experimental Procedure

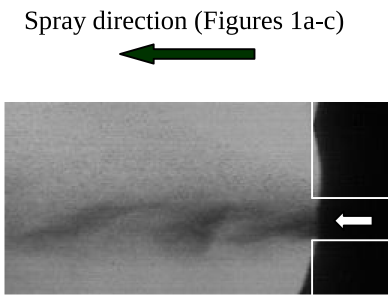
Near-orifice sprays due to actuation of HFC134a-ethanol placebo mixtures from a commercial pMDI actuator package were imaged using laser-based high-speed visualisation. To enable the tests to be performed the mouthpiece of the pMDI was removed. Near-orifice sprays and internal propellant flows were also imaged for a transparent, rectangular model of the expansion chamber and actuator orifice of the commercial actuator. This model was made from a central layer of aluminium sandwiched between two plates of polycarbonate. The aluminium was finely polished to achieve a satisfactory seal with the polycarbonate plates. The valve stem was accommodated in a special seating arrangement that mimicked its asymmetric position with respect to the expansion chamber of the pMDI. The system comprised a copper-vapour laser as the illumination source in conjunction with a Kodak HS4540 high-speed digital camera for image recording. The laser provided a pulsed light source with a frequency of 9kHz. Fibre optic light delivery was used to provide front and backlighting. The camera provided 256 x 128 pixel resolution images and was operated with a Nikon 115mm focal length microlens through a bellows arrangement to image the expansion chamber and near-orifice region. The canister was actuated manually.

Results

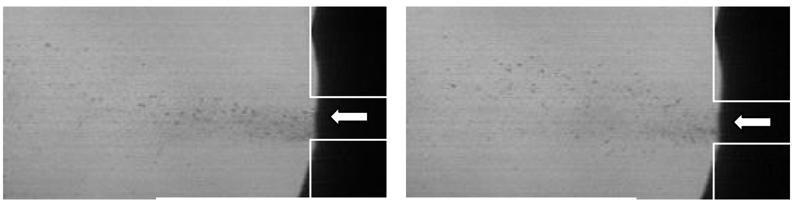
Figure 1 shows a selection of images of the spray in the near-orifice region of the commercial actuator package. Metered dose inhalers produce highly transient sprays as a consequence of time variations of the pressure and liquid mass fraction in the valve stem and expansion chamber upstream from the actuator orifice. During the first 1-2ms of the spray event some liquid enters the valve stem where the pressure is atmospheric. Thus, the liquid is superheated and flash evaporation takes place. This produces a vapour-only spray (not shown in Figure 1). During the next 5-10ms, a vapour-liquid spray with rapidly increasing density is formed. This constitutes the fully developed phase of the spray event (duration approximately 60-70ms). The bulk of the spray is a dense mass containing very fine droplets, but much larger droplets are formed at the edges of the spray. Pulsations of the spray density in the near-orifice region are clearly observed. Each pulsation causes a large fluctuation of the instantaneous spray cone angle. The visualisations show that the dense phase of these pulsations involves a pattern of two to four density waves. Dense spray and lean spray episodes are found to alternate with a frequency around 500-1000Hz. This process is accompanied by the ejection of pulses of large droplets. Versteeg and Hargrave (2001) report similar pulsations in the far-field of a pMDI spray and give some transient velocity maps measured with digital particle image velocimetry (DPIV). Careful analysis of video sequences shows that many of the large droplets have appreciable radial velocity components and that they appear to be produced as a result of a rotating flow structure in the actuator orifice. During the latter half of the spray event (final 60-70ms) the propellant runs out. This causes the spray density to reduce, but the proportion of larger droplets increases. These visualisations reveal that the near-orifice spray formation process of a pharmaceutical pMDI is quite complex.



(a) sequence of four images at 0.11ms separation showing spray pulsation



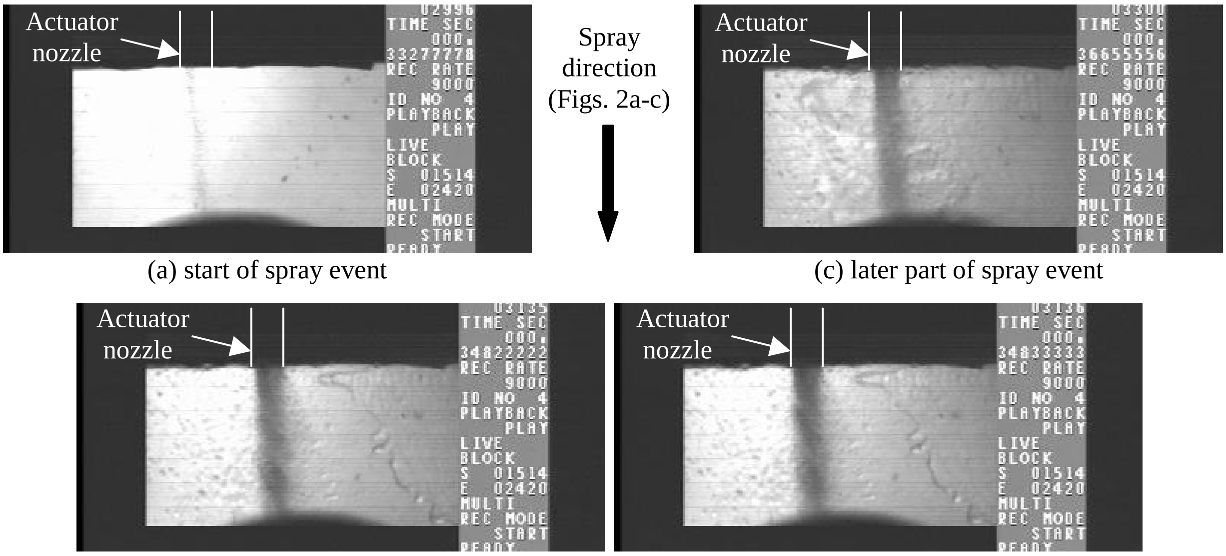
(b) detail highlighting density wave structure



(c) lean spray at end of actuation event highlighting large droplet formation

Figure 1: Visualisations of near-orifice spray of commercial pMDI

The second part of our investigations involved visualisation of near-orifice sprays and internal propellant flow for the rectangular model. The aim of this work is to identify precursor flow events inside the expansion chamber with potentially significant impact on near-orifice spray formation. First, we examine the near-orifice spray produced by the rectangular model to verify that its characteristics are sufficiently similar to those of the commercial pMDI. Figure 2 shows a selection of images of the spray in the near-orifice region of the rectangular model. The duration of the external spray event was found to be shorter (around 100ms, instead of 140ms for the commercial pMDI), but the development of this spray follows the same general pattern as the commercial pMDI.



(a) start of spray event

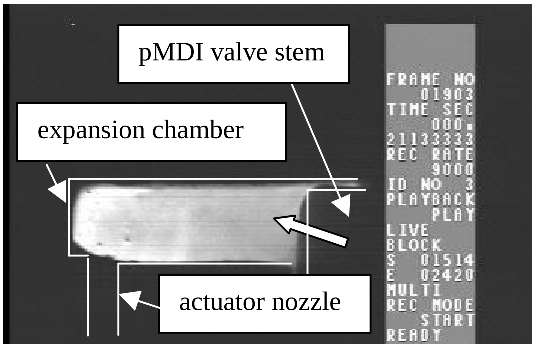
(c) later part of spray event

(b) mid-actuation spray structure highlighting density waves

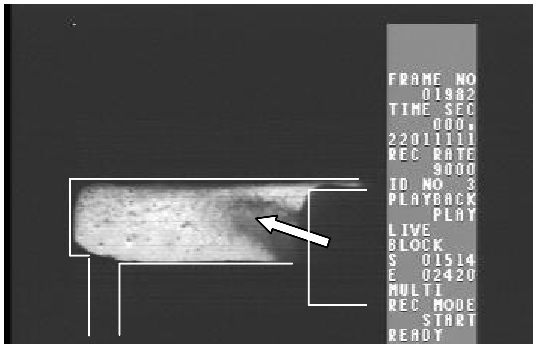
Figure 2: Visualisations of near-orifice spray of rectangular model of pMDI

Next, we consider the internal flow inside the expansion chamber of the rectangular model. Figure 3 shows a selection of backlit images of the flow inside the model actuator. During the first few milliseconds of the actuation event the propellant emerges as a fine droplet mist (Fig. 3a) to displace the air and fill the expansion chamber. After about 10ms the mist suddenly clears and liquid starts to enter the expansion chamber (Fig. 3b). The mass fraction of the fluid in the expansion chamber rapidly increases during the next 15-20ms until the expansion chamber is almost filled with liquid, except for a vapour core (Fig. 3d). The liquid phase appears as a foamy two-phase mixture and light transmission is gradually blocked as the expansion chamber fills up. In this sequence of visualisations the foamy mixture enters the expansion chamber at an angle of about 45^o with respect to the valve axis, due to the asymmetry of the position of the valve stem with respect to the expansion chamber. Examination of the video images shows that the precise direction of the liquid foam flow varies from test to test and also in time within a given test. In all cases, however, most of the liquid stays in contact with the walls and executes a bulk tumbling motion around a vapour-filled core.

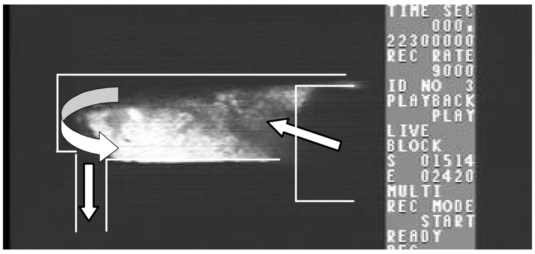
The initial wave of liquid follows a highly curved path along the side and back walls. Next, it continues downwards towards the base of the expansion chamber. In this region, some of the liquid evaporates initially and the remainder is turned upwards along the front wall of expansion chamber, which contains the actuator orifice. Here, part of the liquid flows out of the expansion chamber along with vapour to form spray in the near-orifice region and the rest continues upwards along the front wall of the expansion chamber (Fig. 3c). The upward flow eventually loses momentum and mixes with new fluid entering the expansion chamber, which completes the tumble motion. Light transmission recommences during the final phase of the spray event (Fig. 3e-f). The reduction of the liquid flow rate entering causes the liquid contents of the valve stem and expansion chamber to evaporate or to flow out. Towards the end of the spray event the liquid enters intermittently, with bias towards the front wall at this stage and eventually the liquid flow ceases entirely. The last visible flow structures consist of small quantities of vapour, which are probably formed due to evaporation of liquid remnants of the valve and expansion chamber walls.



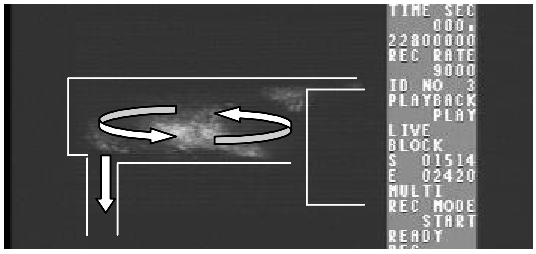
(a) droplet mist fills expansion chamber at start of actuation



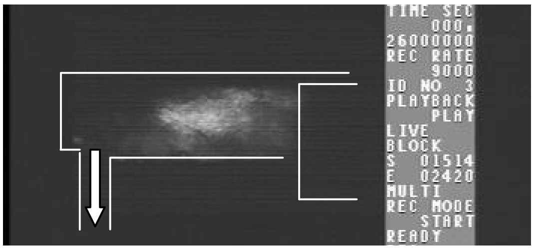
(b) liquid droplets and foam enter expansion chamber



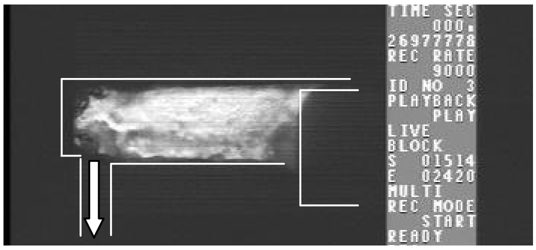
(c) liquid fills base of expansion chamber



(d) fully developed spray phase: liquid fills entire expansion chamber



(e) later stage of actuation event – increase of vapour content of expansion chamber

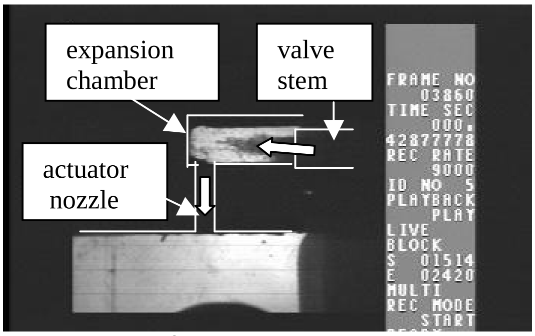


(f) end of actuation –final evaporation of expansion chamber contents

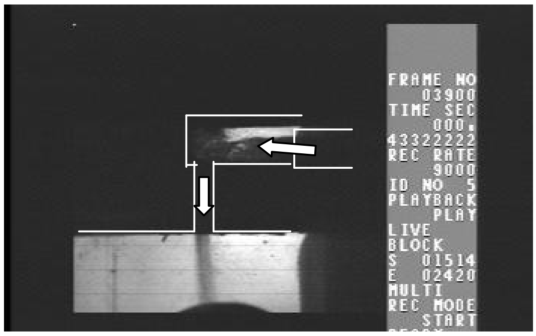
Figure 3: Visualisation of flow regime inside expansion chamber of rectangular model of pMDI

Figure 4 shows sample images with simultaneous views of the flow inside the expansion chamber and the spray in the near-orifice region. A very lean external spray was found to commence as soon as a small quantity of two-phase mixture had built up in the expansion chamber (Fig 4a). As the expansion chamber fills up (after about 20ms) external spray is formed more or less continuously and reaches a fully developed state (Figs. 4b-c). This phase starts when the expansion chamber is filled with liquid, so that liquid is continuously available in the vicinity of the inlet of the actuator orifice. This spray pattern exists for a further 30ms. Then the mass fraction of liquid in the expansion chamber starts to decrease because the metered dose is exhausted. The spray now weakens (Fig. 4d).

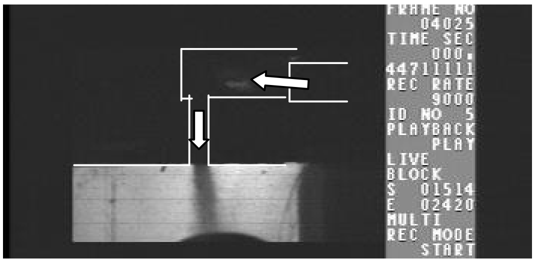
The results in Figure 4 allow us to make connections between internal flow regimes and external spray formation processes. Large droplets emerge in the upper and lower regions of the actuator orifice. This is probably associated with the annular flow regime in the expansion chamber involving a propellant vapour core surrounded by a foamy liquid film that partially covers the chamber walls. As we have noted above, a significant fraction of the wall film that covers the expansion chamber will flow directly into the actuator orifice along with vapour. Even though the flow regime inside the actuator orifice was not visualised, the initial conditions imposed by the expansion chamber flow suggest that liquid films will also be formed along parts of the actuator orifice wall. The film will be stretched by the accelerating flow into ligaments towards the end of the orifice. In turn, these ligaments break up into droplets in the near-orifice region.



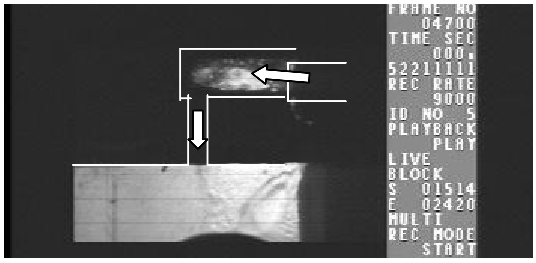
(a) start of actuation event – expansion chamber filling, very lean spray



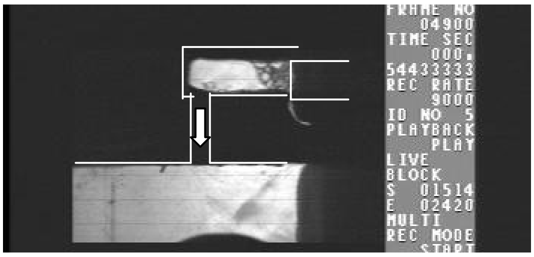
(b) fully developed spray – expansion chamber filling



(c) fully developed spray – expansion chamber full



(d) late stage of actuation event – increasing vapour mass fraction and pulsating lean spray



(e) end of spray event

Figure 4: Simultaneous visualisation of internal flow and external spray for rectangular model pMDI

Given the large upward movements of liquid across the inlet of the actuator orifice it is possible that the film is frequently interrupted by liquid slugs that temporarily occupy a large part or all of the orifice cross-section. Pulsations of the external spray are clearly evident in the video sequences. These correlate with chaotic pulsations of the gas/liquid propellant flow inside the expansion chamber. This intimate connection between the internal flow regime and the spray formation process provides a new explanation for pMDI spray pulsation and density waves. Further research is required to confirm the general correlation between internal flow events and external spray pulsations. Nevertheless, our study suggests that structural features of the external spray of a pMDI may be driven by unsteadiness of the foamy wall film in the expansion chamber due to liquid inertia effects.

Conclusions

The nature of the transient flow and primary atomisation processes of pharmaceutical pMDIs was studied using laser-based high-speed imaging and image analysis. The results highlight the complexities of the valve flow. Visualisations of sprays in the near-orifice region of the commercial pharmaceutical pMDI actuator package revealed the following spray characteristics: (i) start-up transient, (ii) fully developed spray with slow spray density variations with a characteristic time scale around 100ms related to changes of pressure and vapour mass fraction of the two-phase mixture inside the actuator valve and expansion chamber and (iii) rapid spray density pulsations with large droplet production and considerable spray cone angle variations with characteristic time scale around 2ms. The concentration of larger droplets around the top and bottom edges of the spray strongly suggests that an annular liquid flow is present inside the actuator orifice.

External visualisations for the rectangular model pMDI showed very similar spray characteristics. Imaging of the propellant flow inside the expansion chamber of the rectangular model revealed the existence of an annular flow regime with a vapour core and an unsteady wall film consisting of foamy liquid. Simultaneous visualisations of the internal flow and the near-orifice spray allowed us to establish links between the flow regime in the expansion chamber and the nature of the external spray, in spite of the lower resolution of the relevant visualisations. The expansion chamber flow regime was found to induce large variations of vapour mass fraction in the actuator orifice with obvious consequences for spray formation processes at the exit of this orifice. Pulsations and density waves that are found in the external spray of a pMDI appear to correlate with unsteadiness of the foamy wall film in the expansion chamber due to liquid inertia effects.

Knowledge of the pre-atomisation mechanisms in two-orifice systems is crucial for improved control of the external spray characteristics and improved drug delivery efficiency of pharmaceutical pMDIs. Our results highlight the potential of optical diagnostics in the development of improved accounts of the state of the flow inside a pMDI valve and its relationship with drop formation. Further work to image the flow inside the actuator orifice at higher resolution is in progress to examine the suggested spray formation mechanisms in more detail.

References

Clark A.R. "*Metered atomisation for respiratory drug delivery*", PhD Thesis, Loughborough University of Technology, Loughborough, UK, (1991).

Clark, A.R., "Physics of Aerosol Formation", J. Aerosol Med., Vol. 9, Suppl. 1, pp.S-19 – S-27, (1996).

Dunbar C.A., "*An experimental and theoretical investigation of the spray issued from a pMDI*", PhD Thesis, UMIST, Manchester, UK, (1996).

Dunbar, C.A., "Atomization mechanism of the pressurized metered dose inhaler", Part. Sci. Tech., Vol. 15, pp. 253-271, (1997[a]).

Dunbar, C.A., Watkins, A.P., Miller, J.F., "Theoretical investigation of the spray from a pressurized metered-dose inhaler", Atomization and Sprays, Vol. 7, pp. 417-436, (1997[b]).

Fletcher G.E. "*Factors affecting the atomisation of saturated liquids*", PhD Thesis, Loughborough University of Technology, Loughborough, UK, (1975).

Versteeg H.K and Hargrave G.K., "Inhaled air and aerosol particle flow characteristics in a model of the human upper airway", Paper 162, Proc. 4th Int. Conf. on Particle Image Velocimetry, Goettingen, Germany, Sept 17-19, (2001).

Solomon, A.S.P., Shuen J.-S., Zhang, Q.-F., Faeth, G.M., "Measurements and predictions of the structure of evaporating sprays", J. Heat Transfer, Trans. A.S.M.E., Vol. 107, pp. 679-686, (1985).