

INVESTIGATION OF ELECTROSTATIC PROPERTIES OF PHARMACEUTICAL PROPELLANTS

Ву

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Declaration

I, Hussein Ahmad, hereby declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

Abstract

This study addresses the intricate field of measuring electrical volume resistivity in hydrofluorocarbons, specifically focusing on the measurement and application of resistivity in pharmaceutical propellants. Presented research introduces a novel method to measure resistivity in propellants used in metered-dose inhalers (MDIs) for respiratory diseases. It also scrutinizes the influence on the generated current in hydrofluorocarbon liquids produced by different valve stem materials and flow rates.

The initial part of this dissertation provides an in-depth review of the resistivity cell designs, developed over the past three decades, emphasizing the practical aspects of cell design and highlighting the development of cells for testing the resistivity of refrigerants in liquid phase under high pressures. This review succinctly addresses contemporary standards, limitations, and constructional details of both academic and commercial cells and intends to serve as an instrumental guide for future researchers aiming to develop custom resistivity cells for dielectric liquids. It also looks into fundamentals of electrostatic charge and charge transfer as well as into previous research about electrostatic charge influence arising from the interaction with inhaler materials, inhaler designs and drug formulation. It explores measurement methods of abovementioned charge in previous studies.

Further, this thesis examines the practical application of measuring the DC volume resistivity of pharmaceutical propellants like R134a, R152a, and R227ea, which are significant in treating respiratory diseases like asthma via metered-dose inhalers. The study elucidates the relationship between the electrical charging of aerosols, valve stem materials and the delivery efficiency of medicaments to the lungs, emphasizing the role of resistivity in this mechanism.

Overall, this thesis integrates theoretical foundations with practical developments to advance the field of electrical volume resistivity measurement in liquid hydrofluorocarbons as well as their interactions

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with various polymer surfaces, offering significant contributions to the understanding of resistivity in refrigerants and pharmaceutical propellants and proposing innovative solutions to overcome the limitations of existing technologies.

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List of Abbreviations

ρ	Electrical resistivity (Ω m)
σ	Electrical conductivity (S/m)
К	Ionic mobility (m s ⁻¹ (V m ⁻¹) ⁻¹)
q	Volume charge density (C m ⁻³)
1	Current (A)
V	Voltage (V)
R	Resistance (Ω)
J	Current density (A/m ²)
Ε	Electric field strength (V/m)
L	Distance between electrodes (m)
A	Cross-sectional area of material under test (m ²)
V	Velocity of ions (m/s)
D	Molecular diffusion coefficient (m ² /s)
Ν	Number density (m ³)
е	Elementary charge (C)
<i>k</i> _b	Boltzmann constant (J/K)
Т	Absolute temperature (K)
A	Stokes radius of an ion (m)
Н	Dynamic viscosity (Pa s)
n	Concentration (m ⁻³)
K _R	Recombination constant
K _D	Dissociation constant
ε	Permittivity of the material (F/m)
λ	Debye length (m)
u	Fluid velocity (m/s)
t	Time (s)
$ ho_f$	Fluid mass density (kg/m ³)
Р	Pressure (Pa)
g	Acceleration due to gravity (m/s ²)
σ _m	Moleon conductivity (S/m)
R	Particle radius (m)
Δ	Dielectric loss angle

Tan δ	Dissipation factor
ω	Angular frequency (rad/s)
Aτ	Constant related to the nature of ions in a liquid
Eac	Activation energy (eV)
n _o	Unperturbed concentration of particles
i _i (t)	Capacitor charging current component (A)
<i>Ι_ρ(t)</i>	Polarisation current component (A)
i _{ss} (t)	Space charge current component (A)
i _c (t)	Conduction current component (A)
ta	Time duration of DC voltage step (s)
tr	Time duration of resorption current (s)
i _d (t)	Discharging current component (A)
i _{dp} (t)	Depolarisation current component (A)
i'ss(t)	Space charge current component at the discharge state (A)
<i>r</i> ₁	Radius of inner electrode of a concentric cell (m)
<i>r</i> ₂	Inside radius of the outer electrode of a concentric cell (m)

Chapter 1 Introduction

1.1 Static resistivity cell

1.1.1 Introduction

Metered dose inhalers (MDI) are the most popular form of medical inhalers used in the world and the most frequently used system to treat diseases including asthma and chronic obstructive pulmonary disease (COPD) [1]. These afflictions are estimated to affect more than 500 million people globally with millions of people dying as a result of these illnesses every year [2]. Thus, pressure metered dose inhalers (pMDI) plays a crucial role in improving the health of almost 8% of the world's population and saving millions of lives. pMDI are widely used in pulmonary drug delivery compared to dry powder inhalers (DPI) and nebulizers. They are more popular because of being relatively inexpensive, can deliver multi-dose and their ease of use. The essential components of a metered dose inhaler are: propellants, formulation, metering valve and actuator. All these components play a role in delivering the desired drug aerosol to the lung. Schematic diagram of a typical pMDI is shown in Figure 1.1.



Figure 1.1 Schematic diagram of the basic components of a typical pMDI

The canister containing the formulation is located inside the actuator. The metering valve holds a known amount of the mixture of propellant, API and excipient (typically between 25 - 100 μ L) ready to be released and provides nearly 50-250 μ g of drug. The main purpose of having the metering valve is to deliver a reproducible amount of drug to the patient during repeated actuation. By depressing the

canister inside the actuator, the valve stem slides through the metering valve and pressurized formulation passes through the valve stem, actuator sump and actuator orifice.

When the pMDI is actuated, flash boiling occurs and the stationary liquid rapidly turns into a two-phase flashing flow to reach thermodynamic equilibrium at atmospheric pressure. When the formulation is released, a spring returns the valve stem to its original position and the metering valve is refilled because of the gravity, ready for the next shot. The aluminium containers (containers) must withstand a pressure of about 1.2 MPa. The inner surface of the canister should be coated with appropriate material to avoid drug adhesion due to electrical charge or chemical degradation.

The actuator is a plastic housing used for holding the container. It includes a barrel like structure that surrounds the container, a sump, actuator orifice, and the mouth piece as shown in Figure 1.1. It is generally made from polypropylene. The actuator orifice is an integral part of the MDI design, which contributes to control of droplet size distribution of the aerosol released from pMDIs. The diameter of the actuator orifice ranges from 0.14 mm to 0.6 mm. The lengths of the actuator sump and actuator orifice have been proven to affect spray pattern, particle size distribution, and plume temperature of pMDIs.

The formulation used in pMDIs can be either solution or suspension. Either type contains the propellant that can be (HFA134a/ HFA227ea/ HFA152a), active pharmaceutical ingredient and excipients. Suspension MDIs contain micron-sized drug particles suspended in the propellant, while in solution MDIs the drug is dissolved in the propellant using a co-solvent. Some well-known excipients used are: ethanol, water, glycerine, oleic acid, and menthol. Each of these excipients has its own functionality; for instance, ethanol is being used to solubilize drug in the propellant while oleic acid is being used as dispersive agent.

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High vapour pressure of the propellant mixture leads to generation of a high velocity spray out of the MDI actuator orifice and disintegration of the liquid propellant to fine respirable-sized droplets. The expanded spray contains millions of highly volatile droplets and lasts nearly 0.1-0.5 s. Velocity of the HFA pMDI sprays has been reported to be nearly 30 m/s at the mouthpiece and between 2.0 and 8.4 m/s at 10 cm distance from the nozzle.

The gas propellant in most cases makes up more than 99% of the delivered dose, therefore its properties are critical in delivering an effective treatment [3]. Chlorofluorocarbons were initially the most commonly used propellant for MDIs until discovering their damaging effects to the ozone layer leading to their use being curtailed. Hydrofluoroalkanes were introduced as an alternative propellant and are now used in almost all pMDIs. Koura's Zephex HFA 134a propellant is the most widely used propellant in the world, present in more than 70% of MDIs [4]. With the increasing need to limit the effect of climate change in recent years, there has been growing evidence to the global warming potential of HFAs and HFA 134a in particular, thus subjecting the propellant to increasing regulatory scrutiny. This has led the company to develop HFA 152a, a propellant that has been shown to produce emissions which are almost 12 times lower than its HFA-134a counterpart [5]. To overcome regulatory challenges in adopting the newly developed propellant, a better scientific understanding of its properties and effectiveness is needed. Thus, the electrostatic properties, which forms a part of this understanding, must be confirmed. It has been recognised that when the aerosols are delivered by pMDIs, they are electrically charged and consequently the medicament deposition in the human lung is influenced by the level and polarity of charge. If an understanding of the charge acquisition mechanism can be achieved, it may be possible to control the characteristics of the aerosol after exiting the inhaler to ensure site specific lung deposition of the drug. The process of charge acquisition during aerosol formation is poorly understood. All the components of pMDI (canister, sump, actuator orifice, mouth piece, HFA propellant, API in the drug and excipient) will play a role in charge generation. Most of these components of the device are made from plastic materials which are dielectric (insulating). The charge

acquisition mechanism is complex as the contact and tribo-electrification will take place and it is difficult to identify which of these mechanisms is dominant at which location. This complex process depends on the electronic work function of the surfaces involved. Furthermore, the flash boiling that takes place within the valve stem and valve orifice will play a major role in the atomisation process. The net electrical charges of aerosols generated by inhaler devices have been measured by the well-known Faraday Pail measurement. The aerosols emitted by these devices are always bipolarly charged. During the past decade there have been a few attempts to measure the bipolar charge of aerosols generated by pMDIs. In order to better understand the complex charge acquisition mechanisms, a systematic study of the materials and processes involved needs to be carried out. If deep knowledge of the mechanisms involved can be understood, it would then be possible to even control the charge-to-mass ratio of the aerosol so that specific site lung deposition of the API may be achievable.

1.1.2 Aims of research

The project aims to:

- Investigate the charge acquisition mechanisms of hydrofluoroalkane (HFA) propellants in pressurized metered dose inhalers (pMDIs).
- Understand the role of materials and processes involved in charge generation.
- Develop a pressure resistivity cell to study the resistivities of HFAs 134a (1,1,1,2,tetrafluoroethane), 227ea (1,1,1,2,3,3,3-heptafluoropropane), 152a (1, 1-difluoroethane).
- Investigate the influence of ethanol and water on the resistivity of HFAs 152a, 227ea, 134a.
- Determine the possibility of replacing HFA134a/HFA227ea by HFA 152a in pMDIs due to its reduced carbon footprint and improved chemical stability.

1.1.3 Specific objectives

To meet the aims of the research project, specific objectives have been set and are detailed as follows:

- Develop a pressure resistivity cell to study the resistivities of HFAs R134a, R227ea, R152a.
- For a given applied potential, monitor the current flow between the two concentric electrodes.
- Calculate the resistivity using the cell constant.
- Repeat the measurements with differing amount of ethanol and water added to the HFAs.

1.2 Flow-through cell

1.2.1 Introduction

The motion of drug formulations from the canister to the nozzle, in MDIs, is studied. The MDI acts as an atomiser which generates an aerosol via mechanical actions. When aerosols are produced the droplets or particles existing within the generated aerosol clouds mostly act as electrostatic charge carriers. Practically, a lot of atomisation processes generate charged spray with varying levels of electrostatic charge on droplets. Usually, the charge level is observed to appreciate in a considerable manner with a corresponding increase in the energy of the atomisation process. The aerosols produced by the MDIs are often characterised by particles of varying sizes in a dispersed phase and they are invariably electrically charged. The natural charging that take place can be highly complex involving mechanisms such as hydrostatic and hydrodynamic effects. The processes of charging during atomisation of an MDI may include liquid dropping leading to charging of drops (which is also known as the Kelvin Effect), electrification as a result of friction of the liquid at the nozzle (that is, the streaming current), and electrification due to splashing [6]. Electrostatic charges are also built up within the MDI chamber as atomisation occurs. The built up charges also influence the migration of electrostatic charges by the fluid via convection. This migration causes streaming current in the fluid.

Measurements of streaming currents and streaming potentials are critical methods to analyse the zeta potential of surfaces, which is the electrical potential difference between bulk liquid and stationary liquid layer attached to the surface, and they are essential in colloid and interface science, environmental science, medicine, and other applications [7]. Values of streaming current can be measured at different concentrations of formulations and the zeta potentials can be calculated from the results. Researchers have shown that these concentrations influence the outcomes of the streaming current and the zeta potential. With an initial increase in concentration, there is a corresponding increase in the streaming current and the zeta potential until a maximum value is reached, then an inverse relationship occurs. In addition, at low levels of ionic concentrations, there is a tendency for the ions to be adsorbed onto the surface of the inner wall of the tube, pipe, or capillary. However, as the concentration of ions increases there is a saturation point at which the specific adsorption attains. At this point, the counter ion adsorption becomes predominant, causing a decrease in the positive charge density on the wall. Consequently, there is a resultant decrease in the streaming current and the zeta potential.

For years, the electrification during the flow of insulating liquids through pipes has been researched upon. Various models are developed with respect to the influence of flow parameters and pipe dimension for different conditions and have been added to the body of knowledge. The occurrence of

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electrostatic charges on surfaces as well as charges in liquid due to liquid flow has been observed during energy production [8], droplets sliding on a surface [9], liquid flow caused by erosion [10], and hydrocarbons moving through metallic tubes or pipes [11]. Even though this phenomenon was observed and studied extensively and some theories were proposed to explain it, those theories often lack an agreement with experimental results [12]. Also, though, different empirical laws and theories of flow electrification have been developed for the pipe geometry [13], a comprehensive examination on the effect of fluid flow rate, propellant concentration and material choice of the pipe on electrification in MDIs has not been fully explored. A factor that needs to be thoroughly considered is that various theoretical laws have been stated in the open literature, particularly the dependence of the streaming current on the average fluid flow velocity, which varies from linear progression in the case of laminar flow, to a quadratic profile in turbulent cases. Therefore, the choice of appropriate physical model is usually complicated due to the fact that charging is highly dependent on surface chemistry of the inner walls of the tube or pipe the fluid is flowing through, and this is affected by other factors such as formulation concentration, however, it can be influenced by the flow itself by altering near surface ion distribution in a double layer and, as a consequence, chemical equilibrium and interfacial chemistry. These complex factors are the rationale behind the acceptance of different models, which often differ partially by scaling exponents [12].

1.2.2 Aims of research

The study intends to examine the electrostatic properties of MDI propellants and the influence of varying valve stem material type and electrostatic effects of fluid flow rate of the propellant. It will also investigate the development of a flow through system to model the design of MDIs, and the corresponding effect of the design on the electrical currents. In order to achieve that the effect of flow rate of different propellants on the currents, generated as the propellants flow through different plastic tube materials, as well as the effect of different MDI valve stem materials on electrical currents, generated by different propellants flowing at different velocities, will be examined. Results will allow to

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determine optimum valve stem material – propellant combinations in terms of current generated at different flow rate.

Chapter 2 Literature review

2.1 Static resistivity cell

Abstract

This chapter provides a comprehensive review of the expansion of applications involving hydrofluorocarbons has generated a demand for devices capable of measuring the electrical volume resistivity of such liquids across diverse operating conditions. The narrow operating range of commercial offerings, particularly in regard to pressure, compels researchers to develop custom cells for the desired test conditions. A review of resistivity cell designs developed over the past three decades is presented. Academic studies in the past have focussed on the development of cells for the purpose of testing the resistivity of refrigerants in liquid phase under high pressures. The fundamental principles underlying resistivity measurement are discussed while emphasis is placed on practical aspects of cell design. The review addresses facets including contemporary standards, limitations and constructional details of academic and commercial cells. It should serve as a guide for future researchers attempting to develop custom resistivity cells for dielectric liquids.

2.1.1 Introduction

The electrical volume resistivity of dielectric liquids is an important parameter that offers information on the insulating ability, purity and behaviour of a liquid in the presence of an electric field. Resolving the resistivity of dielectric liquids has therefore become an important requisite for multiple industrial applications. Dielectric liquids serve to suppress arcing and corona discharge as well as functioning as coolants and electrical insulators. Determining the resistivity permits one to identify and test the performance of such liquids when used in high voltage applications including transformers, capacitors, cables and high voltage switchgear [14]. The advantage of usage liquid dielectrics in high voltage applications lies in self-healing. The conductive trace, which is left in solid dielectric during electrical breakdown and which makes it unusable, disappears in insulating fluid. Likewise, the widespread use of hermetic and semi-hermetic compressors in refrigeration has created a demand to verify the dielectric properties of the refrigerants used in these systems and to test potential alternatives where high resistivities are required [15]. More recently, identifying the resistivity of dielectric liquids has piqued the interest of the pharmaceutical industry where dielectric hydrofluorocarbons (HFCs) are widely used as propellants in metered dose inhalers. The resistivity of these propellants impacts the charge characteristics of the active pharmaceutical ingredients delivered to patients thereby affecting drug deposition in the lungs. Determining the resistivity of these HFCs is therefore critical to understand their suitability and effectiveness as inhaler propellants [16]. Besides, these applications constitute only a handful of examples where dielectric liquids are currently used. As such, there is a demand for performing resistivity tests across a wide range of operating conditions. Unfortunately, commercial resistivity cells, as of present, only accommodate the needs of the power industry due to market forces where they're designed to test the specific chemical profiles of the liquids used in this industry. These include a small number of oils comprising mineral, ester and silicone. This forces academics to develop their own cells when investigating the resistivity of alternative liquids, especially when said liquids require operating pressures outside that of atmospheric conditions. Herein a comprehensive review of studies and factors concerning resistivity cell design is presented.

2.1.2 Theory of electrical resistivity

The volume resistivity of a dielectric liquid is the quotient of the applied electrical field strength and the current density [17]. It's an intrinsic property that measures a liquid's ability to resist the flow of electric current and depends on the test conditions when performing the measurement. A material with a high resistivity denotes the lack of free electrons, ions and ion forming particles as well as indicating the presence of a low concentration of electrically conductive contaminants. It can be used to analyse the deviation of a material from the desired dielectric characteristics [17]. It's represented by the symbol ρ with an SI unit of Ω m. Resistivity is equal to the reciprocal of the electrical conductivity σ , with the latter having an SI system unit of Siemens per metre (S/m). The volume resistivity may be expressed as:

$$\rho = \sum_{i} \frac{1}{k_i q_i} \tag{1}$$

where the medium possesses charge carriers of species *i* with mobility k_i and volume charge density of q_i . The resistivity of a dielectric liquid is considered to be representative only when the liquid is at thermodynamic equilibrium where the measuring conditions don't significantly affect the mobility and density of the charge carriers [18]. When this condition is satisfied, the dielectric acts as an RC parallel circuit where the conduction current is equal to I = V/R under an applied voltage *V*. The current density **J** can be expressed as:

$$\mathbf{J} = \frac{\mathbf{E}}{\rho} \tag{2}$$

when ohm's law is obeyed by applying a low enough voltage so that the electric field *E* doesn't disrupt the thermodynamic equilibrium. Thus, by measuring the current flowing through a cell one can derive the value for the resistivity of the liquid. In a case where the cross section is uniform and the electric field and current density is constant, the resistivity for a material between parallel plates can be calculated from the resistance using the equation:

$$R = \rho \frac{L}{A} \tag{3}$$

which rearranges to:

$$\rho = \frac{V}{I} \left(\frac{A}{L}\right) \tag{4}$$

where

R = ResistanceL = Distance between electrodesV = Voltage ρ = ResistivityA = Cross-sectional area of material under testI = CurrentThe term $\left(\frac{L}{A}\right)$ is referred to as the cell constant with SI unit m⁻¹. It's a geometrical factor used to convertthe measured resistance to a resistivity value. Although, the true value of the cell constant can only bedetermined experimentally via calibration with liquids of known resistivities. The geometrical surfacearea of electrodes for liquid dielectrics in the absence of fouling is always lower that of electrochemicalarea, where electron transfer takes place [19]. The explanation of this fact lies in the presence of themicroscopical roughness on the surface of the electrode, which effectively increases a surface area of

2.1.3 Nature of charge carriers and mobility

It is believed that in dielectric liquids including those of high purity, low concentrations of impurities are present in the range of parts per billion [20]. The charge carriers in these liquids, at relatively low electric field strengths, are ions that result from the spontaneous dissociation of these impurities as opposed to electrons due to the life time of electrons being very short (lower than 10^{-4} s) [18]. The velocity of ions **v** in a liquid at rest with a constant temperature can be expressed by:

$$\mathbf{v} = k\mathbf{E} - D\frac{\nabla n}{n} \tag{5}$$

with ionic mobility k, molecular diffusion coefficient D and ion number density n. The first term represents the contribution due to ionic drift while the second accounts for molecular diffusion. Molecular diffusion may be neglected at ambient temperature when the applied electric field is above the order of 0.025 V/m [21]. The diffusion coefficient equates to:

$$D = \frac{k \cdot k_B T}{e} \tag{6}$$

where *e* is the elementary charge, k_B is the Boltzmann constant and *T* is the absolute temperature. Ions draw neutral molecules toward themselves according to solvation and are more extensively solvated with smaller ionic radii. Ionic mobility is proportional to the net charge of the particle and inversely proportional to the Stokes radius *a* of the ion (effective radius of solvated ion). When a solvated ion moves with a constant drift velocity after being accelerated by an electric field, it is subject to equal and opposite drag force, which is proportional to dynamic viscosity η , and coulomb force [22]. Drag force, $\mathbf{F} = 6\pi\eta a \mathbf{v}_{\infty}$, is represented by the sum of its normal contribution, also called form drag $2\pi\eta a \mathbf{v}_{\infty}$, and tangential contribution, also known as friction drag $4\pi\eta a \mathbf{v}_{\infty}$.

Thus, the ionic mobility can be expressed as:

$$k = \frac{e}{6\pi\eta a} \tag{7}$$

The simplest model of conductivity at low electric field strengths is based on the assumption that an impurity (electrolyte) in the form of ion pairs AB with concentration n_{AB} is dissolved in a dielectric liquid. This electrolyte dissociates into cations A⁺ and anions B⁻. The global equilibrium reaction between the monovalent ions A⁺ and B⁻ and the neutral AB molecules may then be expressed by:

$$AB \stackrel{K_D}{\leftrightarrow} A^+ + B^- \tag{8}$$

 K_R in Equation (8) represents the recombination constant and K_D the dissociation constant. The number of ions generated is equal to those that recombine at thermodynamic equilibrium causing K_{D^v} the dissociation constant for electrolyte AB at the concentration v, to equal $K_{R^{n+n-}}$ with $n \pm$ denoting the ionic densities [22]. Thus, $n_+ = n_- = \sqrt{K_{D^v}/K_R}$ and conductivity may be expressed as:

$$\sigma = (k_+ + k_-)e\sqrt{\frac{K_{D^\nu}}{K_R}}$$
(9)

 K_D increases when the applied electric field strength increases while K_R is independent of the electric field and can be approximated with relative confidence by Langevin's expression for ionised gases:

$$K_R = (k_+ + k_-)\frac{e}{\epsilon} \tag{10}$$

where ϵ is the permittivity. The steady-state current-voltage characteristics for a given liquid resulting from field enhanced disassociation can then be drawn by making a number of assumptions. These include the lack of injection, diffusion and fluid motion (including electrohydrodynamic convection), instantaneous discharge of ions at the electrodes and an ohmic regime being observed where the field is uniform across the interelectrode gap [22]. The initial current density is then given by:

$$\mathbf{J}_{0} = \sigma \mathbf{E} = (k_{+} + k_{-})e_{\sqrt{\frac{K_{D}v}{K_{R}}}} \cdot \left(\frac{V}{L}\right)$$
(11)

2.1.3.1 Interfacial phenomena at the electrodes

It is commonly assumed that an ideal behaviour of ion neutralisation at the electrodes is observed which is generally not the case. They may experience a delayed discharge and develop a unipolar charged layer that is released upon field reversal. Moreover, the immersion of a solid (electrodes) in a liquid causes a spontaneous unipolar layer of ions near the solid to develop where the thickness of the noncharged neutrality region is given by the Debye length λ :

$$\lambda = \sqrt{\frac{(k_+ + k_-)\epsilon kT}{e\sigma}}$$
(12)

which depends on the surface properties of the solid and the liquid. The measured resistivity of a liquid is lowered if the two layers converge as a result of a high λ relative to the electrode gap [22]. At the electrode boundaries, the non-charge neutrality region in the vicinity of the electrodes is known as the electrical double layer. This consists of two parallel layers of charge surrounding the electrodes. It includes the first layer, the surface charge, where ions adsorb onto the electrodes as a result of electrostatic interactions and a second diffuse layer of ions experiencing a coulomb force toward the surface charge. The extent of net charge and penetration depth into the liquid volume of the double layer are determined by ion migration, convection and diffusion. The accumulation of charge at the electrodes causes enhanced local electric fields to be developed at the interface [14]. The local electric field at the electrodes may also be amplified in practise due to the presence of microasperities at the electrode surface where highly polished surfaces such as steel and aluminium contain microasperities per cm² of the order 10⁸ and an average radius of curvature below 2 µm. This field enhancement is important in studies relating to electrical breakdown as breakdown initiates where the field is largest [21].

2.1.3.2 Electrohydrodynamic convection

Electrohydrodynamic (EHD) effects on the resistivity may also need to be considered. EHD convection can develop in the dielectric due to coulomb forces on the net space charge and is usually observed in dielectric liquids with high concentrations of impurities ($\rho \leq 10^{14} \Omega m$) [21], [14]. EHD may be generated due to charge injection, charge depletion and motion of unipolar charged layers which are explained in more detail in Section 6.3. It causes turbulent fluid flow to occur leading to convection currents in addition to conduction currents. Diffusive currents can be considered negligible, therefore in an ohmic regime; the current density may be expressed by:

$$\mathbf{J} = \sigma \mathbf{E} + q \mathbf{u} \tag{13}$$

with charge density q and fluid velocity **u**. The first term in equation (13) represents conduction current while the second denotes convection current. The governing EHD equations for an ohmic model of resistivity with incompressible, viscous and homogenous dielectric liquids are the following:

$$\nabla \cdot \mathbf{u} = 0 \tag{14}$$

$$\rho_f \left(\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} \right) = -\nabla \mathbf{p} + \eta \nabla^2 \mathbf{u} + q \mathbf{E} - \left(\frac{E^2}{2} \right) \nabla \epsilon + \rho_f \mathbf{g}$$
(15)

$$\nabla \cdot (\epsilon \mathbf{E}) = \mathbf{q}, \quad \nabla \times \mathbf{E} = 0 \tag{16}$$

$$\frac{\partial q}{\partial t} + \nabla \cdot (\sigma \mathbf{E} + q \mathbf{u}) = 0 \tag{17}$$

where *t* is the time, ρ_f is the fluid mass density, p is the pressure and **g** is the acceleration due to gravity [21]. Equation (14) describes the motion of incompressible fluid in the system under consideration. Changes in pressure, fluid velocity and influence of charged particles on fluid motion are obtained from solving Navier-Stokes equation (15). Since the model considers a system, consisting of dielectric fluid with electrolyte, interaction between charged particles in the flow as well as electric charge conservation must be included which is accomplished by using equations (16) and (17), respectively. The contribution of EHD to the conductivity of a dielectric liquid is usually considered negligible below an applied field of the order 10⁵ V/m [23]. This means that EHD may affect the results attained when applying electric field strengths recommended by international standards, since recommended field strength are of the order 10⁵ – 10⁶ V/m (see Table 2.1), depending on the liquid properties and electrode material. Contemporary standards relating to liquid resistivity measurement have not yet addressed this issue.

2.1.3.3 Conduction due to small particles

In dielectric liquids, charge transport may also emanate from small particles known as moleons leading

to a contribution to the current. The main source of moleons in resistivity tests is attributed to the introduction of fresh electrodes into a cell where their removal is considered difficult even with vigorous flushing. The equation for moleon conductivity is given by:

$$\sigma_m = 2\pi^5 \epsilon^2 r^3 n_0 / 27\eta \tag{18}$$

where r is the particle radius and n_0 the unperturbed concentration of particles. This relation may not always correlate with experimental data, particularly for cases with EHD characteristics [21].

2.1.4 AC and DC resistivity

The current measured in a resistivity cell, and for that case any plane capacitor, when applying a DC voltage step of duration t_a in order to energize charge carriers that drift towards electrodes after voltage is applied. It can be expressed as a time variable component $i_1(t)$ equal to the sum of four disparate conduction processes:

$$i_1(t) = i_i(t) + i_p(t) + i_{ss}(t) + i_c(t)$$
(19)

where $i_i(t)$ is the capacitor charging current component, $i_p(t)$ is the polarisation current, $i_{ss}(t)$ is the space charge current component and $i_c(t)$ is the conduction current component.



Figure 2.1 General form of time variation of current through a capacitor with (t_a) and without (t_r) an applied voltage [24]

The charging current $i_i(t) = \epsilon A \partial E / \partial t$ in a capacitor under DC is equivalent to the displacement current and is reduced to zero when the potential difference across the capacitor reaches the source voltage, immediately after t_0 . The current measured prior to t_0 is therefore usually disregarded [24].

The polarisation component represents the current caused by transient charge-carrier drift processes due to ions being attracted to or repelled from electrodes based on their polarity.

Space charge is a concept where charge is treated as a continuum of charges distributed within a volume inside the dielectric as opposed to point like charges. The space charge current component for a capacitor may be a result of charge injection from the electrodes, electrical double layers or dielectric ionisation depending on the electric field strength [25]. This current reduces to zero after a limited time as the charge carriers are neutralised at the electrodes or become trapped in a localised state within the dielectric [24].

The conduction current is a voltage independent component that is characterised by the inherent resistivity of the dielectric medium. It is dependent upon the chemical nature of the dielectric - the type and number of charged species, the chemical reactions they undergo and their velocity [21, 24].

The resistivity of the dielectric at any given time *t* can be found by subtracting the resorption current (current measured after switching off the voltage) from the absorption current (current measured after voltage is applied) when applying a DC voltage. The resorption current is a transient component described by the sum of three other components:

$$i_2(t) = i_d(t) + i_{dp}(t) + i'_{ss}(t)$$
⁽²⁰⁾

where $i_d(t)$ is the discharging current component, $i_{dp}(t)$ is the depolarisation current component and $i'_{ss}(t)$ is the space charge current component at the discharge state. The polarisation and space charge components of the DC resistivity are time varying and reduce to zero after a long enough measurement time leaving the steady-state component corresponding to the conduction current. On the other hand, the AC resistivity is only composed of two components, a steady state conduction component that is independent of frequency and a frequency dependent component [24] [26].

AC voltage sources are often used to determine the conductivity of liquids with high conductivities. This is because the use of AC limits the presence of "polarisation" effects due to ion drift by causing the ions to oscillate with the applied frequency about their positions, preventing them from accumulating at the electrodes. Lower frequencies are typically used with higher resistivities as polarisation effects are less significant [19]. However, the use of AC, when measuring the resistivity of dielectric samples with low conductivities, is limited by the presence of large capacitive currents relative to the resistive current, preventing the latter from being measured accurately [27]. Relaxation time of solution is inversely proportional to the conductivity. Since conductivity is low in dielectric liquids, its relaxation time is larger

than the cycle time of applied current. As a consequence, capacitive reactance of the cell decreases with respect to its resistance making capacitive currents larger than resistive currents.

IEC 60247 and ASTM D1169 standards advise readers to measure the resistivity at the 'steady state' as opposed to the initial 'true resistivity'. The true resistivity of the fluid can only be found immediately after applying the voltage with low voltages, which can be accomplished with an AC voltage source as stipulated by IEC 61620. Polarisation processes (induced electric dipole moments) take place as soon as the voltage is applied and within seconds, an initial resistivity can be measured according to IEC 61620 as conduction currents become dominant. Conversely, IEC 60247 and ASTM D1169 propose the use of relatively high voltages for a protracted time [17]. The steady state in materials is typically arrived at within 60 seconds where the resistivity is determined according to IEC 60247 and ASTM D1169 (see Table 2.1), while it may take longer for materials with high resistivities [28]. Thus, the type of voltage source is an important consideration when deciding on the type of resistivity intending to be measured.

2.1.5 Standards for resistivity measurement of dielectric liquids

There exist different international standards for measuring the resistivity of insulating liquids including IEC 61620, IEC 60247 and ASTM D 1169. The fundamental differences between these standards relating to resistivity measurement are summarised in Table 2.1.

Standard	IEC 61620:1998 [29]	IEC 60247:2004 [17]	ASTM D1169-19 [30]
	Insulating liquids –		Standard Test Method
		Insulating liquids –	
	Determination of the		for Specific Resistance
	Determination of the	Management	for specific Resistance
		Measurement of	
Title	dielectric dissipation		(Resistivity) of Electrical
		relative permittivity,	
	factor by measurement		Insulating Liquids
		dielectric dissination	
	6 .1 1	dielectric dissipation	
	of the conductance and		

Table 2.1 Standards relating to the measurement of dielectric liquid resistivity [28
--

	capacitance – Test	factor (tan δ) and d.c.	
	method	resistivity	
	Dielectric dissipation	Relative permittivity,	
	factor (resistivity	dielectric dissipation	
Quantities	measurements simply a	factor (tan δ), DC	DC resistivity
	means of dissipation	resistivity	
	factor determination)		
	Resistivity is related to	DC resistivity is related	DC resistivity is related
	an initial current density	to "steady-state current	to a current density "at
Definition	during a short period of	density".	a given instant of time".
	time.		
Mathad	Current measurement,	Current measurement,	Current measurement,
Wethod	trapezoidal voltage	DC voltage	DC voltage
Field strength	≤ 100 kV/m	≤ 250 kV/m	0.2 to 1.2 MV/m
	0.4 - 5 s (trapezoidal		
	square wave, f = 0.1 to 1	1 min	1 min direct polarity / 5
Electrification time	Hz rise time 1 to 100		min short circuit / 1 min
	mc)		reversed polarity
	1115)		

IEC 61620 is intended to offer guidance on the determination of the dielectric dissipation factor and was not designed to standardise resistivity measurement. However, an approach for measuring the initial resistivity is outlined as a means of measuring the dissipation factor based on equation (16):

$$Tan \,\delta = \frac{1}{\epsilon \omega \rho} \tag{21}$$

where δ is the dielectric loss angle whose tangent is the dissipation factor and ω is the angular frequency [29]. The resistivity value is sampled at the flat current level of every half period using a trapezoidal square wave voltage (frequency = 0.1 Hz to 1 Hz, rise time = 1 ms to 100 ms). This frequency and time range is IEC 61620 standard which has been suggested by International Electrotechnical Commission to measure initial resistivity during short time of ions energization and, as a consequence, those time and frequency ranges have been chosen for this study. This short energization can be observed after voltage is applied ions drift electrodes with characteristic transition time. The use of low electric field strengths, below 100 kV/m, is proposed in the standard and an electrification time between 0.4 and 5 seconds. The resistivity is defined as being related to an initial current density within a short time of energisation. Nonetheless, the steady-state resistivity is different from the initial resistivity measured using the method proposed in this standard and it's impossible to establish a relationship between these two quantities [28].

IEC 60247 relates DC resistivity to a steady-state current density and the outlined method for measuring the resistivity involves measuring the current through the insulating liquid after applying a DC voltage. The maximum field strength proposed in this standard is 250 kV/m with a suggested conventional arbitrary time of electrification of 60 seconds [17].

ASTM D 1169 [30] relates DC resistivity to a current density "at a given instant of time". The standard proposes for current to be measured after a DC voltage is applied at a field strength between 200 kV/m and 1.2 MV/m with an electrification time of 60 seconds. It also suggests to average two measurements with both polarities to compensate for effects relating to polarity, however, research has shown for this to not be enough of a conditioning where a number of subsequent polarity reversals is required [28].

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2.1.6 Factors that influence the resistivity of dielectric liquids

2.1.6.1 Moisture

The conductivity of pure water is 6×10^{-6} S/m at 25°C. It dissociates to H+ and OH- which gives rise to the stated conductivity value. It contributes free charge carriers to the sample therefore serving to reduce the measured bulk electrical resistivity [31]. This is exhibited in Figure 2.2 where the DC conductivity of insulating liquids (hydrocarbons) increases with the amount of moisture. A water content of 20 ppm in new mineral oil can lead to an order of magnitude increase in conductivity [32], [33].

The presence of water is an important factor that affects the electrical strength of insulating liquids where even "0.01% water in transformer oil reduces its electrical strength to 20% of the dry oil value" [34]. The severity of the impact of moisture on the dielectric properties of a medium depends on the solubility of water in the liquid and the relative saturation. Dissolved water has a lower impact on the resistivity than emulsified or free water. The solubility of water in a liquid is defined as the total amount of water capable of being dissolved at a particular temperature. The dependence of solubility on the temperature follows an exponential relationship [35].



Figure 2.2 Effect of Water Content on the Conductivity of Hydrocarbon Liquids. [33]
2.1.6.2 Temperature

Resistivity has an inverse dependence on the temperature that is generally exponential [17]. This makes it important to ensure that measurements are made under precise temperature conditions. The dependence of resistivity on the temperature is largely due to the temperature dependence of the liquid viscosity. Increasing the temperature increases the motion of the charge carriers and lowers the viscosity of the liquid causing an increase in the mobility of the carriers. It also increases the number of charge carriers due to the dissociation coefficient increasing. This leads to a higher conductivity in the sample. The product of the mobility of ions in highly insulating liquids and viscosity is approximately constant as the temperature is varied according to an empirical relation known as Walden's rule:

$$k \cdot \eta \sim 10^{-11} \ (m^2/Vs) \tag{22}$$

It denotes the fact that mobility depends on the temperature to the same extent as the viscosity. The viscosity is therefore inversely proportional to the mobility which allows an expression to be derived relating the temperature to the conductivity for most insulating liquids:

$$\sigma(T) \approx A_T e^{(-E_{ac}/k_B T)}$$
(23)

where T is the absolute temperature in Kelvin, A_T is a constant related to the nature of the ions in the liquid and E_{ac} (eV) is the activation energy [32].

2.1.6.3 Electric field

The conductivity of insulating liquids when measured with increasing electric field leads to an established trend that may be visualised graphically in Figure 2.3. The graph can be separated into three regions (numbered in the figure as 1, 2 and 3) including an initial ohmic region with low field strength where the current density is proportional to the electric field. This is followed by a region with an

intermediate field strength where current density appears to be saturated. Finally, a region with large field strengths is observed where the current density increases rapidly with electric field before resulting in electrical breakdown.



Figure 2.3 Shape of the current-voltage graph for a dielectric liquid [36]

The field strength dependence of the resistivity can be explained by ion drift and generation processes. Ions can be generated in the bulk via disassociation and at the electrodes via injection. In the initial low field region, ions migrate to the counter electrode due to the force from the electric field where they accumulate or are partly neutralised. Free ions are generated by the electric field and can be replaced by newly generated ions in the dielectric leading to a constant resistivity value. At higher field strengths, the ion drift velocity increases. The intermediate field region involves free ion density decreasing as they are displaced at a faster rate than they are generated. Thus, the current density enters a saturated state where the dissociation and recombination rate stay constant and the resistivity increases with increasing field strength. During the high-field region, the ionic disassociating rate increases to an extent where the rate becomes independent of the applied voltage leading to more charge carriers and decreasing resistivity with field strength [28], [32]. In this region above the saturation voltage, charge is also injected from the electrodes contributing to the increase in charge carriers and conductivity. Charge injection upsets the thermodynamic equilibrium so that the resistivity varies with position and time [14]. One such method of injection is Schottky emission, which involves thermionic emission of electrons from a metal electrode into the conduction band of the liquid, enhanced by reducing the work function with an electric field and correcting for the image force. Another method involves a process called Fowler-Nordheim field emission where electrons migrate to the liquid from the surface of a metal electrode via quantum mechanical tunnelling under high electric fields (above $\sim 10^8$ V/m) [21]. Injection is dependent upon the impurities present in the tested medium, the nature of the liquid (including polarity) and the electrode material [22]. It usually becomes dominant only at applied electric fields above 100 kV/m [37]. The current density in the steady state will also become space charge limited if the injected charge density is high [22].

2.1.7 Resistivity cell types and requirements

High range resistivity cells may be categorised into two basic groups according to their geometric designs including a parallel plate arrangement and a concentric cylinder arrangement. A cylinder cell is considered more favourable in most cases and has been adopted by commercial entities as a result. Some academic studies, however, have utilised the parallel arrangement citing the desire to investigate the effect of a variable inter-electrode distance or due to the simplicity of the design. The important parameter, which characterizes distance between the sensing elements and the surface area of the metallic piece and its contribution into electronics circuitry, is cell constant defined as length to area ratio. It will be used further to compare various types of resistivity cells and to assist in designing resistivity cell.

The main appeal behind the cylinder arrangement is the lower cell constant offered when measuring a similar volume of fluid to a parallel cell. This is a result of the higher surface area of the electrodes that are exposed to the liquid in a cylindrical cell. A lower cell constant allows one to increase the measuring range of the cell, reduce the volume of liquid required for measurement and reduce the size of the cell. The equations for the cell constant in each case offer a mathematical rationale for the existence of lower cell constants inherent in cylinder cells where:

$$\frac{\ln\left(\frac{r_2}{r_1}\right)}{2\pi L} \tag{24}$$

is the equation for the cylinder case and

$$\frac{L}{A}$$
 (25)

for a parallel cell where *L* is the distance between the electrodes, *A* the cross-sectional area of the measuring electrode (in parallel cells) while r_2 is the inside radius of the outer electrode and r_1 is the radius of the inner electrode (in a cylinder cell). The natural logarithm in equation (24) possesses a relationship where the range tends to zero exponentially as the ratio $\left(\frac{r_2}{r_1}\right)$ tends to 1. Thus, for a set difference between r_2 and r_1 , we may exponentially reduce the size of the cell constant in cylinder cells by linearly increasing the diameters of the concentric cylinders. Increasing the length of the cylinders and area of the measuring electrode in a parallel cell also reduces the cell constant linearly in both cases, as can be seen in matrices (24) and (25). The dimensions result in volume and materials increasing proportional to the length for a cylinder and proportional to the square of the plate dimension. An exponential increase in size is thus required for parallel cells to reduce the cell constant in the same way a linear increase in cylinder length reduces it. This is not ideal in the parallel case due to possible size and volume constraints.

The design of the cell must also meet certain requirements to perform satisfactorily as outlined in the aforementioned international standards. It should allow the component parts to be cleaned easily and thoroughly. It should permit the cell to be used at the required constant temperature and offer a way to measure and control the temperature of the liquid. The materials used in constructing the cell should

be capable of withstanding the temperatures and pressures intended to be applied. In addition, the electrodes' surface in contact with the liquid should have a smooth finish to ensure easy cleaning. The measuring electrode should also be guarded to facilitate a high order of measurement accuracy by limiting any erroneous impact of fringe fields [17].

The fringe field effect is when part of the measuring field falls outside the geometric space of the measuring volume and can lead to a mismeasurement of the fluid resistivity as a result. The use of a guard electrode serves to absorb the current flowing through the fringe field, ensuring a homogenous field while confining the current to a defined area and limiting interference with the field lines. An inhomogeneous electric field causes the resistivity to be a function of spatial coordinates rather than being representative of the bulk medium [38]. Therefore, it is important to ensure a homogenous field within the measuring volume to obtain a representative value for the resistivity. This is another reason why it is recommended that the surface of the electrodes be smooth to limit electric field amplification caused by rough surfaces.

Likewise, the insulating materials incorporated in the cell should not absorb or be affected negatively by the test liquids or solvents used for cleaning. The resistivity of these insulating materials must also be high, especially the material used between the measuring electrode and the guard. Examples of insulating materials that are considered satisfactory for such a purpose include borosilicate glass, steatite, boron nitride, TFE-fluorocarbon and quartz [30]. Additionally, the electrode material must be corrosion resistant and introduce no errors under the conditions of the test. Stainless steel is often recommended for this purpose [17].

2.1.8 Previous studies – resistivity cell design

Resistivity cells developed by academics have largely been designed for the purpose of testing the resistivity of liquid refrigerants. These refrigerants have to be pressurised under large pressures to

maintain a liquid phase at room temperatures due to their low boiling points. As a result, the cells they develop mainly focus on delivering a similar performance to that of commercial cells while maintaining a large pressure within the cell. Although, the need for large pressures within the cell places considerable emphasis on ensuring effective evacuation of the system prior to tests to prevent water vapour from condensing into moisture in order to avoid the influence of water on electrical properties of refrigerants under study. The measurement process therefore becomes more complicated than that used in commercial cells as nitrogen purging and vacuum pumping are typically employed. Unfortunately, the aforementioned standards do not offer procedural information on the measurement of resistivity for dielectric liquids under large pressures. Thus, the lack of a standardised method for limiting the presence of moisture when conducting such resistivity tests may be a source of variation for results attained by related studies. Table 2.2 lists a selected number of studies into the resistivity of liquid refrigerants including the type tested, the results attained and details about the cells used in the studies. The following sections summarise the selected studies including those that utilised parallel plate cells initially followed by studies involving concentric cylinder cells.

Study	Fellows B. et al. (1991)	Bryan J. & Seyed- Yagoobi J. (1996)	Meurer C. et al. (2001)	Feja S. (2012)	Dschung F. & Kindersberger J. (2016)
Type of power source	AC & DC	DC	AC	DC	DC
Design	Concentric cylinder cell	Concentric cylinder cell	Parallel plate cell	Concentric cylinder cell	Parallel plate cell

Table 2.2 Summary of key parameters for selected studies into the resistivities of refrigerants

Refrigerant	(1) R134a, (2) R152a	R404A*	R134a	(1) R134a, (2) R152a, (3) R744	(1) R134a, (2) R227ea
Resistivity (liquid phase, saturation pressures, ≈25°C**)	(1-DC) 6.6 x 10 ⁸ Ωm, (1-AC) 1.8 x 10 ⁶ Ωm (2-DC) 2.2 x10 ⁷ Ωm, (2-AC) 5 x 10 ⁵ Ωm	3.1 x 10 ⁷ Ωm	1.089 x 10 ⁶ Ωm	(1) 10 ⁸ Ωm, (2) 10 ⁷ Ωm, (3) >10 ¹⁴ Ωm	(1) 6 x 10 ⁶ Ωm, (2) 1.3 x 10 ⁸ Ωm
Cell constant	Not known	0.1901 m ⁻¹	1.02 m ⁻¹	0.113 m ⁻¹	4.35 m ⁻¹

 ** The temperatures used in these studies varied between 20 $^\circ$ and 26 $^\circ$

2.1.8.1 Resistivity cell, designed by Meurer S.

The cell used by Meurer et al. [15] was a parallel plate cell displayed in Figure 2.4 with a measurement electrode surrounded by a guard and a 2 mm interelectrode gap. Epoxy was used to separate the measuring and guard electrodes. They tested the AC resistivity of different refrigerants and used a low 50 mV voltage with a frequency of 1 kHz after experiencing the dissociation-field effect at higher voltages with some of the refrigerants. The refrigerants tested in the study include R404A, R407C, R410A, R507 and R134a. The measurements were conducted between temperatures of 23°C and 26°C in liquid phase at saturated pressures and the cell was flushed with nitrogen and evacuated prior to each measurement. The total error of each resistivity measurement was assumed to be a maximum of 15% due to the tolerances of the structural parts. The cell possesses a relatively large cell constant of 1.02 m⁻¹ compared to Feja S. (2012) with 0.113 m⁻¹ which may be a significant factor behind why the resistivity measured for R134a is two orders of magnitude lower than that measured by Feja S. (2012). The large cell constant may be attributed to the use of a parallel plate cell compared to a concentric

cylinder cell where the latter is capable of attaining lower cell constants when measuring the resistivity of similar volumes of dielectric liquid.



Figure 2.4 Parallel plate cell design utilised by Meurer et al. (2001) [15]

2.1.8.2 Resistivity cell, designed by Dschung F. and Kindersberger J.

The test cell used by Dschung and Kindersberger [39] was a parallel plate cell consisting of modified stainless steel flanges mounted to both ends of an aluminium pipe with an inner diameter of 100 mm and gaskets installed between the pipe and flanges. The cell is shown in Figure 2.5. Coaxial bushings were used to connect the electrodes from outside the cell where the top electrode was connected to the voltage source. The bushings were able to withstand a pressure of up to 6 MPa and temperatures of up to 100°C. The frame was made of PEEK (Polyether ether ketone) and the electrodes of stainless steel. The measuring electrode had a diameter of 24.2 mm and was glued to a PEEK support structure with PEEK material separating the measuring and guard electrodes by 1 mm. The distance between the measuring electrode and anode was set at 2 mm. The guard ring was connected to the volume limiter which was in galvanic contact with the grounded lower flange. The volume limiter served to reduce the required volume of liquid.





They investigated the DC resistivity of the samples across a range of temperatures. An average field strength of 250 kV/m was applied for 60 minutes with the current in the last 10 minutes being used to calculate the resistivity after a steady state had been fulfilled. They found no clear trend with respect to temperature between the 20°C and 90°C they tested. During their investigation they found R134a showing indications of decomposing when stressed with 250 kV/m after several hours and recommended the long-term stability of the HFC to be proven prior to application. The HFCs were also investigated at commercial grade purity with >99.5% for R134a and >99.0% for R227ea. The procedure used by Dschung and Kindersberger involved scavenging air in the cell before inserting the liquid refrigerant and performing a short test with 500 V to ensure a correct filling level. The measured values allow one to easily discern whether the refrigerant is in its gaseous or liquid state as they differ by orders of magnitude. A manometer was connected to the top flange as shown in Figure 2.5 and was used to monitor the pressure in the cell to ensure a correct amount of refrigerant was in liquid phase. The pressure was used to determine the temperature of the liquid using a temperature pressure correlation. 500 V with a positive polarity was applied for 60 minutes with current recorded every 2 seconds and the

current in the last 10 minutes was used to calculate the resistivity. The polarity was then reversed to negative 500 V while repeating the same process again. This was then all repeated with different temperature values and repeated four times for each refrigerant. The results for the resistivities of the refrigerants as a function of temperature can be seen in Figure 2.6 and Figure 2.7.



Figure 2.6 R134a resistivity results as a function of temperature [39]



Figure 2.7 R227ea resistivity results as a function of temperature [39]

Dschung and Kindersberger [39] use a similar parallel plate design to that of Meurer et al. [15] while exploring the resistivity of the same refrigerant R134A, with a larger cell constant of 4.35 m⁻¹ compared to 1.02 m⁻¹ in the latter. Dschung and Kindersberger [39] also apply a different voltage source, using DC while Meurer et al. [15] make use of AC and achieve a similar value for the resistivity of R134a with the same order of magnitude of 10⁶ Ωm. The effects of this difference in cell constant size and the difference in voltage source applied therefore appears muted in this case. Furthermore, the cell developed by Dschung and Kindersberger [39] uses PEEK material to separate the measuring and guard electrodes by 1 mm compared to Meurer et al. [15] who use a 2 mm interelectrode gap with epoxy as the separating material. The difference in the interelectrode gap in this case is relatively small and should not contribute to any significant difference in the measured electrical resistivity. However, it should be noted that as the interelectrode gap increases, the current measured by the measuring electrode increases proportionally (to an extent depending on the size of the fringe field) due to the fringe field effect leading to a lower resistivity measurement. Both epoxy and PEEK are insulating materials with high enough resistivities to be considered satisfactory.

Similar to Meurer et al. [15], the cell by Dschung and Kindersberger [39] measures a resistivity value for R134a which is two orders of magnitude lower than that measured by Feja S. (2012). The factors causing this may similarly be attributed to the use of a parallel plate cell with a higher cell constant.

2.1.8.3 Resistivity cell, designed by Bryan J. and Seyed-Yagoobi J.

Bryan and Yagoobi [40] used a cylinder cell shown in Figure 2.8 consisting of two cylindrical electrodes enclosed by a housing where they are all electrically insulated from each other and made of 304L stainless steel. The housing serves as a guard electrode and pressure vessel with either nylon 6/6 or Teflon being used as insulators to separate the electrodes and housing depending on the fluid and operating conditions used. Two electrical connections to the cell exist at the base of the device with coaxial cables being used. Three resistive temperature devices, two servicing ports and a pressure port are mounted at the top of the housing. The seals used are fluid compatible O-rings and the cell can be completely disassembled for cleaning. The cell possesses a relatively low cell constant value of 0.1901 m⁻¹ owing to the concentric cylinder geometry. The cross sectional drawing of the cell provided by the author in Figure 2.8 offers little in the way of clarity and is thus difficult to interpret.



Figure 2.8 (a) Image of assembled and (b) cross sectional drawing of resistivity cell [40]

They investigated the DC resistivity of an HFC refrigerant called R404A with a 2.55 mm electrode separation and field strength of 39.2 kV/m. The resistivity was tested over a temperature range between 248K and 283K with a corresponding saturation pressure range of 0.26 MPa to 0.83 MPa. An electrification time of 36 seconds was used after it was determined as the time needed for current to settle with a less than 1% change occurring. The cell was pressure tested to 10.3 MPa and between temperatures of 210K and 350K. A typical test involved cleaning with acetone and evacuating to a 50 micron vacuum before purging with nitrogen gas to remove moisture. The cell was cooled with liquid nitrogen to 250K before inserting the refrigerant. It was further cooled before beginning measurement of resistivity as the cell warmed to ambient temperature at 10 degrees below the lowest temperature of the temperature range. The cell was then heated to 10 degrees above the highest temperature of the

range before starting measurement of resistivity as the cell cooled to ambient temperature. Once a test was completed the fluid was deserviced and the cell was disassembled for cleaning. The time required to obtain the resistivity data for the refrigerant across the temperature range was two days due to the slow change in temperature. The results of the investigation are displayed in Figure 2.9.



Figure 2.9 Electrical conductivity of R404A as a function of temperature [40]

2.1.8.4 Resistivity cell, designed by Feja S.

Feja [41] tested the DC resistivity using a field strength of 250 kV/m. He did not use a guard ring and instead calibrated the test cell with a reference liquid in advance. The test cell was calibrated after each cleaning process with n-Heptane at room temperature. He made no mention of flushing the cell with nitrogen to limit moisture content. The cell has a large proven measuring range that is evidenced by the experimentally determined resistivity of liquid carbon dioxide (R744) at greater than $10^{14} \Omega m$. This aligns well with the fact that cell also possesses the lowest cell constant with a value of 0.113 m⁻¹ out of the studies discussed. A thermostat bath was used to vary the temperature and keep it constant when performing a test. A Pt100 sensor connected to the inner electrode was used to monitor the temperature. The resulting resistivity values for the refrigerants tested across a temperature range are plotted in Figure 2.10.



Figure 2.10 Resistivity results for R152a, R134a and R1234yf plotted as a function of temperature

[41]

A description of the cell has not been offered by the author of the study. At the top of the inner electrode, a white polymeric material can be seen which is thought to be an insulator separating the inner electrode extending toward the bottom and the metal above the polymer, possibly serving as a guard electrode. The surface lining the inside cylinder wall of the metal construction on the right side of Figure 2.11 (a) is considered another electrode. The cell possesses a flange at the top with two cylindrical ports extending from the top of the flange.



Figure 2.11 (a) Inner (left) and outer electrode (right), (b) Assembled test cell [41]

2.1.9 Commercial resistivity cells

The current market leaders in commercial resistivity cell offerings include BAUR GmbH's DTL C and Megger Group Limited's OTD test cell (shown in Figure 2.12). The specifications for each of these cells is summarised in Table 2.3. The OTD and DTL C cells possess similar designs, albeit, a detailed description of the arrangement for the latter cell is not provided by the company. They both measure the resistivity of liquids under atmospheric pressure and do not offer the ability to adjust the applied pressure on the tested liquid. The design of these commercial cells is therefore slightly different from the cells developed by the aforementioned studies accordingly. The OTD has an inner measuring electrode cylinder possessing a hemispherical end being enclosed by a similar larger cylinder acting as the anode. The cell is sealed by a non-conducting glass covering at the top with an orifice where the liquid enters the cells while the guard and measuring electrode are separated. The guard also serves to distance the orifice from the measuring electrode to prevent electric field distortions around the inlet from extending toward the measuring volume and affecting the electric field homogeneity. The introduction of curvature by the hemispherical ends of the electrodes causes a geometrical enhancement to the electric field. This adversely compromises the electric field homogeneity, because the electric field concentrates around curved ends. However, the degree of this enhancement may be limited by a large radius of curvature. Moreover, a drain valve is situated at the bottom of the cylinder where the fluid exits. The cells also enable easy disassembly for cleaning which helps limit the presence of contaminants [42, 43].

Test cell	OTD [42]	DTL C [43]
Measurement range	2.5 M Ω m to 100 T Ω m	2.5 M Ω m to 100 T Ω m
Temperature range	10 °C to 110 °C	11 °C to 110 °C

Table 2.3 Comparison of specifications for OTD and DTL C commercial resistivity cells

DC voltage range	125 V to 500 V	500 V max	
Humidity	< 60% RH	< 100% RH	
Accuracy	± 1% from calibrated	± 1% from calibrated	
Accuracy	value	value	



Figure 2.12 Arrangement of OTD resistivity cell, courtesy of Megger Ltd [42]

2.1.10 Recommendations

When designing a high range resistivity cell, it is recommended to utilise a concentric cylinder arrangement to achieve a low cell constant. This is to increase the measuring range of the cell, reduce the volume of liquid required for measurement and reduce the size of the cell. The measuring electrode should also be guarded to achieve a high order of measurement accuracy by limiting any erroneous impact of fringe fields. The surface of the electrodes should be smooth with no sharp edges to prevent charge injection caused by electric field amplification. In terms of procedural recommendations, moisture content in the cell should be limited by cleaning with a solvent such as acetone or n-heptane and evacuating the cell with a vacuum pump before purging with nitrogen gas.

2.1.11 Conclusion

An analysis of resistivity cell designs has been presented including a description of considerations that need to be addressed when attempting to develop a resistivity cell for insulating liquids, particularly for HFCs used in pharmaceutical metered dose inhalers and industrial refrigerants. The nature of charge carriers and the associated mobility in dielectric liquids is also detailed. An explanation of the guidelines set out by IEC and ASTM standards relating to resistivity measurement of dielectric liquids is offered including the difference between AC and DC resistivity measurement.

Several research studies into the resistivity of dielectric liquids using individually developed cells have previously been published with the majority of these involved in resolving the resistivity of liquid refrigerants. This article therefore summarises the arrangement of these custom cells and the main findings from the studies. It was suggested that a standardised method be developed for dielectric liquid resistivity tests performed under pressure.

2.2 Flow-through cell

2.2.1 Introduction

The combination of drug formulation and design of the packaging components have shown a significant influence on the electrostatic properties of aerosol suspensions ejected from metered dose inhalers [60]. However, to fully understand the electrical properties and behaviour of the formulation contained inside the MDI canister remains a challenge, largely due to the absence of consensus on the mechanisms responsible for charge generation and the associated bottlenecks in evaluating electrical properties of liquefied propellants. Moreover, in order to actively comprehend the electrostatic properties of propellants, it is imperative to gain an insight into the micro-level interactions involving charges between the propellants and the selected materials employed in the construction of the MDI.

The choice of materials with specific electrical properties plays a pivotal role in assessing and optimizing the performance of MDIs. This is important because the highly electronegative nature of most HFC propellants, results in robust interactions between the drug particles and container surfaces [61]. In this context, the adoption of a flow through cell proves valuable in analysing the triboelectrification and streaming current effects within MDIs. These cells provide a controlled environment where the interaction between propellants and valve surfaces can be precisely monitored. One of the primary concerns of materials selection in regard to the design of MDIs is managing the electrical charges generated during inhaler actuation. A careful consideration of the currents recorded with different propellants and the materials used in the MDI construction enables the possibility to mitigate the undesirable effects of flow electrification.

Flow electrification pertains to the phenomenon where electric charge is transferred from the boundary between a liquid, in motion and a solid surface, into the body of the liquid. This transfer happens by forming a layer at this interface. The Debye length, which is the thickness of this double layer plays a crucial role in this process [62]. Various studies have shown that the Debye length is directly proportional to the square root of the electrical resistivity of the liquid. Usually, the Debye length is measured in the order of microns. In an electrical double layer, the first layer or the Stern layer, which is also known as the compact layer possesses charged particles which are firmly bounded the surface of the pipe/tube via physiochemical actions [63]. Its thickness is in the order of a single molecule diameter, which is approximately a few nanometres. Within the layer the charges and ions stay fixed in place. They are not influenced by the movement of the surrounding substance. The second layer, termed the diffuse layer, is comprised of free ions of opposite charge, and their concentration diminishes as one moves away from the solid surface. The diffuse layer is similar to a space charge layer, which balances the charge existing on the solid surface. Here, excess charges and ions have the capacity to be drawn into the bulk flow region, influenced by convection, diffusion, and conduction. The motion of these charged species within the diffuse layer generates a substantial quantity of charges dispersed throughout the

bulk flow region, giving rise to the creation of a streaming current. Hence, this phenomenon is at the core of flow electrification [64].

With respect to the increased charges within the flowing fluid, a streaming current is the sum of the excess positive charges moving within the fluid while the counter negative charges remain stationary on the inner surface of a non-conductive (such as a plastic material) pipe, while the streaming potential is the potential difference measured at current equal to zero generated by the convective flow of charge as a result of pressure gradient, that is, liquid flow, through a charged capillary or membrane [65]. The resulting electrochemical potential can be evaluated at points along the length of the pipe [66]. The assessment of streaming current provides a highly sensitive approach to characterize the zeta potential of surfaces. Streaming current holds significant importance in the domains of colloid and interface science, environmental applications, medical applications, and various other fields. In cases where two noble metal wires are introduced through the wall of the pipe at some distance apart and electrically interconnected, and when the flow and surface charge reach a magnitude capable of inducing a significant potential along the flow path, it becomes possible to measure the streaming current by incorporating an ammeter into the electrical circuit. This method is widely acknowledged as a means of ascertaining the surface charge or zeta potential of the material comprising the pipe. As the electrolyte flows through, a potential drop occurs, with the upstream wire serving as the anode and the downstream wire acting as the cathode in this electrochemical process [67].

2.2.2 Theory of Electrostatic Charge Transport

The field of flow electrification has seen over five decades of research, which has encompassed both numerical investigations and experimental measurements. In its early stages, the research predominantly focused on the study of steady and fully developed flow electrification phenomena [68,69]. These studies often relied on analytical solutions that offered insights into the radial distribution of charge density, assuming certain simplifications. However, these early research endeavours fell short of addressing the evolution of streaming current and the movement of charges along the flow path,

consequently leaving a notable gap in the discourse regarding electrostatic saturation [70]. In flow electrification, the fundamental principle lies in the macroscopic manifestation of the overarching dynamics that govern the motion of charged particles, that include electrons, ions, and charged microclusters. These patterns of movement emerge due to the intricate interplay among convection, conduction, and diffusion processes. Mathematically, these dynamics can be represented in the equation of charge conservation, as depicted in Equation (26) [64]:

$$\frac{\partial \rho_q}{\partial t} + \nabla \cdot \mathbf{J} = 0, \tag{26}$$

In Equation (32) we have, ρ_q representing the charge density and the vector j denoting the density. In engineering scenarios involving flow electrification systems often reach a state where we can neglect the initial term, $\partial \rho_q / \partial t$ in Equation (32). The second term, which involves the divergence of the density provides information about how charges redistributed spatially and their non uniformity.

Typically, the modified Helmholtz Smoluchowski equation (HS equation) is commonly used to establish a relationship between the streaming coefficient (SCC) and important parameters like zeta potential at the solid liquid interface fluid relative permittivity, viscosity and microstructural characteristics of pipes or tube walls in contact. However, to apply this equation effectively it is crucial to determine the length and cross-sectional area of the pipes or tubes involved. This can be achieved through measurements or, by utilizing empirical models [71].

When a pressure gradient is applied over the cross-section of the flowing fluid through the pipe, the relative motion occurs between the fluid and the solid surface. Afterwards, the net ions of the diffuse layers move with the same velocity within the flowing fluid, which generates the streaming current in the fluid. The streaming current coefficient in the flowing fluid can be calculated with respect to a bundle of capillary tube model:

$$C_{sc} = \frac{I_{sc}}{\Delta p} = \frac{A_e}{L_e} \cdot \frac{\varepsilon_0 \varepsilon_r}{\eta} \zeta$$
(27)

where I_{sc} represents the streaming current, Δp stands for the pressure difference applied across the section of the fluid; A_e and L_e are the effective cross-sectional area and length of the contacting pipe, respectively, η represents the dynamic viscosity of the fluid and ζ is the zeta potential. Equation (27) gives the modified HS equation for the streaming current coefficient of a flowing fluid through a pipe/tube [72].

It is necessary to emphasize that the current density in Equation (26) is governed by convection, conduction, and diffusion, and their relationship is stated in Equation (28):

$$\mathbf{J} = \frac{\rho_q}{j_{conv}} \mathbf{u} - \frac{D\nabla\rho_q}{j_{diff}} - \frac{\sigma\nabla\varphi}{j_{cond}}$$
(28)

where the vector **u** represents the velocity of the fluid, *D* denotes the diffusion coefficient, σ stands for the electrical conductivity of the fluid flowing through the pipe/tube, and φ is the electrical potential. The contributions made by convection, diffusion and conduction are represented by j_{conv} , j_{diff} , and j_{cond} , respectively. The effect of the fluid flow on the charge motion is reflected by the j_{conv} . The consideration of the continuity equation (given in Equation (29)) and the Navier-Stokes equation (stated in Equation (30)), as the governing equations, gives further analysis on the fluid flow field:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot \rho \mathbf{u} = 0$$
(29)
$$\rho \frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} = -\nabla p + \mu \nabla^2 \mathbf{u} + \rho \mathbf{f}$$
(30)

In Equations (28) and (29), ρ represents the density of the fluid, p is the pressure exerted by the fluid, μ is the dynamic viscosity of the fluid, and f represents the external force exerted on the fluid. Here, j_{diff} is the contributing factor which is strongly related to the state of the fluid flow. Electric charges migrate from regions of higher concentration to regions of lower concentration in laminar flow, where the diffusion is primarily influenced by Brownian motion. Moreover, the diffusion process is wholly affected by molecular diffusivity, D_m , a fluid constant of $10^{-9} \text{ m}^2 \text{s}^{-1}$. On the other hand, turbulent flow scenarios are characterised with the dominance of turbulent motion perpendicular to the direction of the fluid flow which is superior to Brownian motion, acting as the major driving factor for charge diffusion in the fluid. Accuracy in analysing the effect of turbulent flow on charge diffusion requires the consideration of an additional diffusion coefficient, denoted as D_t .

Previous works have hinged the evaluation of the additional diffusion coefficient on semi-empirical relationships. Nonetheless, a simpler quantitative analysis can be achieved by the adoption of the turbulent eddy viscosity coefficient, v_t . This method provides a more reliable analysis of the effect of turbulent activity in turbulent flow situations. The uneven distribution of the charges caused by the governing turbulent fluctuation in the fluid creates an electric field that affects the motion and the behaviour of the charged particles. Therefore, with respect to j_{cond} , the term measures the impact of the electric field caused by the heterogeneous distribution of charges on the characteristics of these charges [70]. Based on the knowledge of flow electrification process in laminar and turbulent flows through a thermoplastic pipe/tube, a mathematical relationship between the electric potential of the fluid flow and charge distribution within the flowing fluid is required. This relationship can be represented by the Equation (31), based on the Poisson equation:

$$\nabla^2 \varphi = -\frac{\rho_q}{\varepsilon_0 \varepsilon_r} \tag{31}$$

where ε_0 is the dielectric constant in a vacuum and ε_r represents the relative dielectric constant. The charge transport equation can be derived when Equations (1), (3), and (6) are incorporated into each other, to obtain Equation (32):

$$\mathbf{u} \cdot \nabla \rho_q - \nabla \cdot D_m + D_t \nabla \rho_q + \frac{\sigma}{\varepsilon_0 \varepsilon_r} \rho_q = 0$$
(32)

Equation (38) gives a qualitative consideration of the charge density, velocity of the fluid, molecular diffusivity – a property of the fluid, relative dielectric constant – a property of the pipe material. Generally, the equation accommodates two types of factors that influence electrification, that is, the fluid/flow properties and the electrical properties. The fluid/flow properties include geometrical components of the fluid path, the rate at which the fluid flows, and the resistance of the fluid to flow. On the other hand, the electrical factors include electrical conductivity and permittivity, although, operating temperature and material degradation can alter these electrical factors. Furthermore, properties such as material chemical composition and surface topography may influence the charge transport tendency. Ultimately, Equation (38) serves as a theoretical foundation when trying to understand the electrostatic behaviour of drug delivery through MDIs in relation to the material selection for MDI components. Streaming current measurement is a standard method for analysing the surface charge or zeta potential of a pipe material.

2.2.3 Fundamentals of Electrostatic Charges

Typically, there are three mechanisms in which aerosols can obtain electric charges, namely: static electrification; diffusion charging and; field charging. In practice, diffusion and field charging are rare cases experienced in inhalation therapy, other than particular systems that entail liquid electro-hydrodynamic atomization, where an electric field is applied and employed to charge a stream of liquid that contains medication. Surface tension is dealt with, leading to a break-up of the liquid filament to form droplets of uniform sizes based on operating conditions. Conversely, static charging is a general phenomenon, which can be classified as contact charging and frictional charging. Contact charging involves an initial binding between the particles or between the fluid and the surface of the wall of the pipe/tube without rubbing against each other, while frictional charging includes a relative motion of the two surfaces taking place while they are still in contact. Tribo-electrification occurs with either of these forms of static charging.

Acquisition of charges and subsequent charge transfer associated with the formation of aerosols in MDIs are processes that are not fully understood. One of the reasons for this knowledge gap is due to the fact that the general mechanism of contact charging has been solely defined based on differences in work functions for metal-metal interactions which possess electrically conductive surfaces. Contrarily, most suspended particles from MDIs are poor conductors and are effective electrical insulators with surfaces that are difficult to analyse with limited knowledge of their electron energies [72]. Moreover, material surfaces involved in inhaler components, like valve elastomers, canister holder and other add-on devices are mostly thermoplastic polymeric materials that are electrical insulators or possess coated or insulated surfaces such as the case of metal canisters in MDIs [73].

2.2.4 Electrostatic Charge Nature and Material Properties

The tribo-electrification and streaming current of inhaler formulations through MDI devices is largely controlled by interactions between the drug composition and the materials of various components within the inhaler. Given the fact that most MDI packaging components are made of polymers, which are highly insulative materials, there is a high possibility of generating static electricity when they come in contact with each other. The accumulation of static charges occurs as a result of rapid formation of dipole configurations due to corona discharge, making the material act as frozen-in polarised cells or Electrets. Polymeric materials store up charges for extended periods of time, when they are insulated appropriately – a property exhibited by Electrets. The stored charges may be real, that is, a layer of positive or negative charges bounded within the near surface of the polymer or largely dispersed within the bulk of the material, or they may be polarized charges, which can be heterogeneously localized within molecular structures similar to dipole polarization. Therefore, molecular structure may affect the array or orientation of polarized charges in a polymeric material. According to a previous study [74], the use of different valve components with MDI suspensions including salbutamol sulphate and levalbuterol sulphate demonstrated that the type of elastomers and valve stem materials influenced the charge nature of the aerosol. CFC-11/12 propellant blends exhibited charge profiles with varying degrees and

polarities when packaged, employing different combinations of valve container and stem materials. Higher electronegative value was realised in the CFC albuterol aerosols using a stainless steel valve stem compared to acetal counterpart. Conversely, levalbuterol sulphate produced net electronegative charges when passed through nitrile (BK 356) elastomers and exhibited net positive charges when placed in contact with nitrile RB 190NT (BK 357) polymeric material [72].

2.2.5 Electrostatic Charge Dependence on Drug Formulation Composition

Also, an alteration in the drug formulation and propellant concentration may alter the polarity of the aerosol. This is an observation from the product-dependent charge profiles associated with commercial MDI aerosols. Electrostatic charges present in propellants and the charge profile of an inhaler formulation can be influenced by a successive increase in ethanol composition and the addition of inhaler ingredients such as, beclomethasone dipropionate, to the propellant. It has also been found that low positive charges of R134a become highly electronegative as a result of adding salbutamol sulphate particles (a popular inhaler ingredient) to the formulation [75]. This proves that composition profiles significantly contributes to the charge nature of the dispersed aerosol. Furthermore, an impurity, such as water in MDIs may alter the electrostatic characteristics of the aerosol via polarity inversion of the fluid net charge.

2.2.6 Addition of Spacer Device on Electrostatic Behaviour during Drug Delivery

Device configuration also affects the electrostatic behaviour of the propellant. The integration of a spacer device can extend the degree of variability in the available dose as a result of the electrostatic charges on the walls of the spacer component, the size of the spacer device and the type of material used to fabricate the spacer device. A study has shown that the use of a spacer device increased the effectiveness of drug delivery and deposition to the human lungs, and it was also dependent on the type of the impactor inlet [76]. Also, it can mitigate side effects that are associated with oropharyngeal deposition [77]. A spacer device serves as a retaining compartment for MDI aerosol suspensions when inhalation occurs through a valve with a singular passage at a natural flow rate. Plastics are the most

used materials to fabricate spacers, as they are insulative. Therefore, electrostatic charges are produced at ease and piled on the plastic walls via handling. The drug output may be depleted by the interactions occurring between the electrostatic charges and the charged particles present within the aerosol. On the other hand, reducing the charges on the spacer walls may effectively enhance drug delivery [78]. The charges piled up on the surface of the spacer walls may be mitigated by the application of different forms of surface treatments, like the use of coatings on the walls with antistatic linings that are commercially viable [79], or subjecting the surface to priming prior to use [80][81]. The coating of the spacer walls with surfactants is the most typical method adopted. Ionic surfactants are usually more effective than their non-ionic counterparts, indicating that the ionic surfactants enable the spacer walls to conduct these electrostatic charges. Ideally, the spacer is immersed in dilute detergent solution for a period of time then dip-dried without rinsing with water and drying with a towel [82]. Detergent-based treatments extend the aerosol retention time within the spacer by decreasing the amount of deposition on the inner walls of the spacer, increase lung deposition with improved response to drug delivery [83]. All kinds of detergents can spread over the surface of the inner walls to form an extremely thin layer similar to a monomolecular layer [73]. There is a possibility that the hydrophilic portion of the surfactant molecules support the conduction of electrostatic charges of the surface from the wall of the spacer device through the patient to the ground, although, the accurate mechanism has not yet been understood at a molecular scale.

2.2.7 Measurements of Electrostatic Charges

Major variables focused on during the studies of the electrostatic charges in spacer devices are aerodynamic particle size distribution, drug retention within the spacer walls, aerosol residence time, and fine particle dose. Typically, measurements of the electrostatic charges on the spacer walls were not considered, probably due to the fact that most studies concentrated on the improvement of drug delivery. A study reported the measurement of electrostatic charges on the exterior part of the spacer using a static locator at specific points [84], however, the charges within the spacer walls are more

important and different because electrostatic charges are not uniformly distributed across the thickness of the insulator, thus, the surface potentials of the inner surface may not be the same as the surface potentials of the inner surface of the spacer device. Nevertheless, a basic static measurement procedure entails the use of a field-sensing probe that is electrically insulated and identifies the signal of neighbouring surface electrostatic charge in the form of an induced voltage. An attribute of these electrostatic voltmeters is the ability to evaluate electrostatic charge without being in contact with the inner surface of the spacer which may disrupt the measurement, enabling the transfer of charges from the inner walls to the probe. The voltmeters function in such a way that they drive the conductive housing of the field-sensing probe to a specific voltage that is needed to neutralise the electric field existing between the probe and the inner surface. Typically, the voltage measured by the probe equates the undetermined voltage existing on the surface. Therefore, electrostatic voltage probes can be used to obtain a rapid evaluation of the charge sign and intensity on the inner walls of a non-conducting spacer, although the spatial resolution of this method is limited by the physical dimension of the probe

A number of static methods involving the collection and accumulation of electrostatic charges have been widely employed to evaluate electrostatic charges associated with inhaler-produced aerosol particles [74, 86] . In empirical methods involving non-analysis of particle size, total amount of the aerosol is retrieved by directing the fluid to a Faraday chamber, which is made of a metal and contains deposition of particles onto a filter. The filter is usually electrically insulative since the induced charge is the variable to be measured. According to an experiment by Peart et.al [87], a sensitive electrometer was used to record the electric current generated. Faraday chamber electrometers that are commercially available possess sensitivities of 0.001 femtocoulomb (fc), which is suitable for measuring most MDI aerosols. Still, based on the simple technique, only the total net charge can be calculated and no information is retrieved with respect to comprehensive detail on the relationship between the charge and size distribution of the aerosol particles. Irrespective of the limitation imposed by insufficient information, an early study employed the use of glass inlet induction port connected to a singular stage

impactor directly before the electrometer was connected, to allow the collection of only fine particles. The study provided qualitative understanding of reproducible discrepancies in electrostatic characteristics between different chlorofluorocarbon and hydrofluroalkane propelled MDI formulations [87]. The assembly enabled an assessment of the fraction of the fine particles instead of the total net charges of all the particles within the propellant.

The formation of aerosols is complex and it is dependent on the vapour pressure of the propellant and the inclusion of solids, surfactants, and other solvents. When the inhaler is actuated and the contents exerted from the metering chamber are subjected to the ambient pressure [73]. Generally, the pressurised propellant rapidly evaporates when it is in equilibrium with the atmospheric pressure. With this process, there is adequate supply of mechanical energy required to eject the volume of liquid from the actuator and atomise the liquid.

Atomisation involves tribo-electrification, however, there is an uncertainty in understanding the mechanism behind the physiochemical processes that leads to droplet charging [72]. However, all speculated mechanisms involve the separation of negatively charged (anionic) species from the positively charged counterparts (cationic) situated near the surface of the fluid when atomization occurs [73]. Electrostatic charge is essential in the consideration of aerosol formation and subsequent interactions between particles and further interactions between the MDI inner surfaces and the particles.

It is necessary to emphasize that the aerosol formulation exhibits intrinsic electrostatic characteristics after atomization. Specifically, novel HFA formulations used commercially and have been used to substitute their CFC predecessors seem to possess greater electrostatic charge [86]. The differences in charge retention by various formulations that are commercially used have been studied. The work was conducted by using sensitive electrometer connected to a one-stage impactor which served as a Faraday chamber for fine particles, and it was observed that the average net charge with respect to actuation was between 0.27 nC and 0.045 nC [75].

Presently, it is of no record that there is a standard measurement method for electrostatic charges associated with MDI aerosols. There are two classifications for the variety of apparatuses used in studying the electrostatic charges of pharmaceutical aerosols, which are static and dynamic techniques. The movement or induction of charges from aerosol particles to the measuring equipment is associated with the static technique. Some of the methods classified under the static techniques include the Faraday chamber, aerosol electrometer apparatus by Peart et al. [87], electrical low pressure impactor (ELPI) [88], the electrical next generation impactor (eNGI) [89], and the modified twin stage impinge [90]. A common feature to these measurement systems is that aerosol samples are charged with a corona charger. The key interest is to determine the distribution of particle size from electrical signals. Nevertheless, without the use of a corona charger, the internal charges of the aerosol particles may also be measured by the ELPI method. In a study conducted by Glover and Chan [86] there was no noticeable difference in the charge measurement of MDI aerosols when the corona charger was fitted in but switched off and when the charger was not in place. Therefore, the corona charger was detached from the apparatus to prevent a scenario where artefacts occur in charge and mass measurements, resulting from unnecessary tribo-electrification and particle deposition on the charger block. Although, the measurement of particle size and derivatives of electrical variables using the ELPI tends to be an indirect procedure, the method is timely and is simple to employ, being that no physiochemical analyses are needed. In particle charge measurements, the edge of using the modified ELPI over the aerosol electrometer apparatus is the superior resolution of size and charge classifications. Discrepancies occurring in mass and net charge across different fractions of the particle sizes can be measured, nevertheless, a limitation involved is the inability to measure the bipolarity within individual size fraction. However, a primary concern about this classification is that the only variable that can be measured is the net charge for a specific particle size; there is no consideration for a separate measurement of bipolar charges within the specified particle size sample. In the dynamic technique, the primary variable to be considered is the electrical mobility of each particle, rather than the net charge

of a fraction of the population of particles. The electrical mobility of a particle can be defined according to Equation (33):

$$\mu_e = \frac{V_d}{E} = \frac{neC}{3\pi\eta d} \tag{33}$$

where V_d represents the transport velocity of a particle situated in an electrical field, E stands for the magnitude of the electric field, n denotes the number of elementary charges carried by the particle, C stands for the Cunningham slip correction factor, which is the factor that allows for the prediction of the drag force exerted on a particle moving fluid with a Knudsen number within the continuum region and the free molecular flow, η represents the viscosity of air, and d is the diameter of the particle in consideration [91]. Based on the size and charge, a particle shows a unique electrical mobility, which can be evaluated by considering the transport velocity of the particle situated in an applied electric field. The bipolarity existing within an aerosol can be measured due to the fact that the dynamic charge measurement depends on the electrical nature of individual particles. Therefore, this is an edge that the dynamic charge measurement technique has over its static counterpart. Some measurement methods analyse the charge distribution of aerosols by conducting a simultaneous measurement of the particle size and electrical mobility. The electrical single particle aerodynamic relaxation time (E-SPART) analyser [91] and a bipolar charge measurement system are key examples of the dynamic charge measurement methods. The E-SPART analyser takes measurement of the particle size and the particle charge using a Doppler velocimetry. On the other hand, the bipolar charge measurement system measures bipolar charges on pharmaceutical aerosols by operating on the principle of electrostatic precipitation which quantifies the charged particles with respect to their electrical mobility. The method was developed by Balachandran's group at Brunel University, United Kingdom [92]. In some cases it is preferable to rely on a measurement method which allows not to just count particles, but rather to measure charge to mass ratio. Such a need often arises for pharmaceutical aerosols due to dose dependent therapeutic outcome [93]. Bipolar Charge Analyser (BOLAR) offers such an opportunity [94]. Its operation principle

is based on flow division by cutoff particle diameter and divided particles deposition on detection tubes that are different for different charges. Charge to mass ratio is determined after particles deposition is completed and tubes are disassembled. These measurement devices were separately designed and developed by different research groups and work based on different mechanical principles.

Glover and Chan worked using an ELPI method at a flow rate of 30 L/min and observed that different MDI formulations exhibit unique and reproducible electrostatic charge and size profiles [86]. For example, the aerosol obtained from a sample of 10 single actuations of albuterol sulphate suspension formulation blended with HFA-134a propellant (Ventolin-HFA, an equivalent of 100 μ g albuterol base per actuation) showed a net negative charge, independent of the size of the particle. On the other hand, a drug formulation containing fluticasone propionate blended in HFA-134a propellant (Flixotide, 250 μ g per actuation) produced charged aerosols with significant bipolarity. A larger fraction of the mass of active ingredients were particles with aerodynamic diameter larger than 1.0 μ m and possessed negative charges, while particles with smaller diameters carried positive charges. The average net charge of the fine particles (that is, particles with diameters less than 6.6 μ m) was somewhat reproducible as consecutive actuations were compared irrespective of the drug formulation within the inhalers. Despite the observation that there was a slight increase in the magnitude of charge during the service life of the MDI, the authors pointed out that more inhalers will be required to conduct a comprehensive study that will ascertain the statistical significance of the observed trend.

Kwok et al [95] continued on the measurements conducted by Glover and Chan by evaluating the effect of the inhaler's use on the electrostatic charge of the aerosol after actuation. The authors took measurements of charge-size profiles of different MDI drug formulations. The actuations were delivered either as single and distinct actuations, activated at an interval of 1 hour, or continuous actuations with 30 seconds between consecutive actuations. The charge-size profiles were measured for a number of HFA formulations, such as Intal Forte (cromolyn sodium blended in HFA-227 propellant at 5 mg per actuation), Tilade (nedocromil sodium in HFA-227 at 2 mg per actuation), Flixotide (fluticasone propionate at 250 µg per actuation), Ventolin (albuterol sulphate at 100 µg per actuation), and Qvar

(beclomethasone di-propionate blended in HFA-134a at 100 μ g per actuation). The profiles of Intal Forte and Tilade showed a similar trend to that of Flixotide irrespective of the mode of actuation, either singly or continuously actuated. The Flixotide charge-size profile showed a comparable profile to profiles observed by Glover and Chan [86]. Generally, larger particles having aerodynamic diameters greater 6 μ m carried net negative charges, and finer particles showed positive charges. Based on the mass, larger portion of the drug formulation mass were characterized by negatively charged particles, which was entirely contained in particles with aerodynamic diameters greater than 1 μ m. Although a trend was observed which showed increase in positive charge as the particle size decreased within the range of 0.2 – 1.0 μ m, a smaller fraction of the drug mass was involved. Nevertheless, there was a positive net charge associated with particles having aerodynamic diameter smaller than 6.66 μ m and contained the drug. The charge-size profiles obtained by Kwok et al in the case of Ventolin were influenced by the usage of the inhaler, which was contrary to the behaviour of Intal Forte, Tilade, and Flixotide [93]. Continuous mode of actuation showed Ventolin profiles that were unipolar and negatively charged, similar to the trend discussed by Glover and Chan [86]. However, there was a shift of the corresponding profiles toward bipolarity as the aerosols were generated by single and discrete actuations.

The case of bipolarity was also reported by Orban and Peart [96] concerning single actuation profiles, however no information was given concerning the type of drug formulation type. Keil et al [97] also conducted a similar study and stated that aerosols obtained from single mode of actuations of HFA Ventolin exhibited bipolar profiles. In both studies, a fraction of the particle size distribution profiles possessing smaller aerodynamic diameters were characterised by negative charges, while larger particles, which occupied a larger fraction of the mass of the albuterol sulphate carried positive charges. Ultimately, however, the average net charge associated with the finer particles was negative.

Furthermore, a hypothesis was stated by Kwok et al [95] that charge relaxation may have a significant effect on the charging of albuterol sulphate. When actuation occurred, electrostatic charges were produced on the particles, where counter-charges would have been resided in the actuator, the metering valve components, and residue of the formulation deposited at these locations. The counter-

charges require time to decay which may be long enough to influence charging of particles from subsequent actuations, if the time interval between the subsequent actuation is short. Contrary to the formulation, Qvar is a drug formation that contains solution of beclomethasone di-propionate with ethanol acting as a co-solvent blended in HFA propellant with no addition of surfactant [72]. According to the authors, the aerosols produced from single and discrete actuations of Qvar showed a unipolar behaviour with positive charges, with no respect to size [73], and this observation was confirmed by Keil et al [97]. Kwok et al [95] observed that the net charge of fine particles in Qvar showed lower values and were more unstable compared to Intal Forte, Tilade, or Flixotide formulations. The authors indicated that the drug mass in any droplet is directly proportional to the size of the drop in the Qvar formulation based on the fact that the drug was dissolved They hypothesised there is a direct relationship between drug mass and any contributed charge generated from excipients, which establishes their observation of the correlation between specific charge (charge per unit mass of drug) and the size of the particle. Given that the Qvar aerosol projected in the continuous mode was only slightly charged, Kwok et al suggested that there may be an occurrence of charge relaxation for Qvar, similar to the case for Ventolin, and stated that interactions between the drug formulation and the materials used for the metering valve and the inhaler stem may account for the charging process. Therefore, it is apparent that it is not the propellant by itself, but the propellant-drug combination, that determines the charge-size profiles of these drug formulations.

Chapter 3 Liquid Resistivity of Pharmaceutical Propellants using Novel Resistivity Cell

Abstract

Propellants are used in metered-dose inhalers to treat patients with respiratory diseases, including asthma. These devices use propellants to generate pharmaceutical aerosols. But aerosols, containing these propellants, delivered by metered dose inhalers (MDIs), become electrically charged after actuation, and propellants higher resistivities limit charge dissipation, which also limits medicament deposition in the lungs. In order to prevent that, it is necessary to have resistivity values at hand. For this reason the DC volume resistivity of pharmaceutical propellants, including R134a, R152a, and R227ea, was studied in the liquid phase, at saturation pressures and room temperature. These measurements are also very useful for other industries, where those substances are used as refrigerants. The resistivities for the propellants (R134a, R152a, and R227ea) were measured using a novel concentric cylinder-type capacitance cell designed in-house, also described in this chapter, and they were equal to 3.02 x 10^{10} Ω m, 2.37 x 10^{9} Ω m and 1.31 x 10^{10} Ω m, respectively. The electrical resistivity data obtained was found to be at least two orders of magnitude higher than the limited data available in the literature. Challenges regarding the development and performance of the resistivity cell are presented. The experiments focus on the above propellants and their mixtures with different concentrations of ethanol and moisture. Concentrations of water and ethanol for measurements were defined by concentration ranges used in commercial MDIs by pharmaceutical companies. The resistivity of propellant mixtures containing moisture concentrations ranging from 5 to 500 ppm and ethanol concentrations ranging between 1000 and 125,000 ppm was determined. The resistivity was tested across 10-minute and 1-hour periods and was performed in accordance with the contemporary IEC 60247 standard.

3.1 Introduction

R134a (Tetrafluoroethane - $C_2H_2F_4$), R227ea (Heptafluropropane, CF_3CFHCF_3), and R152a (Difluoroethane, $C_2H_4F_2$) are hydrofluorocarbons (HFCs) widely used as propellants in the pharmaceutical industry for metered dose inhalers (MDI) to generate inhalable drug aerosols to treat respiratory conditions. Such HFCs were developed to overcome environmental issues associated with the use of chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs), as the chlorine in those molecules is responsible for the depletion of the ozone layer. Besides their application in MDIs, they are also used as refrigerants [49], [50]. It has been recognised that when these inhalers deliver the aerosols, they become electrically charged. Consequently, the medicament deposition in the human lungs is also influenced by the level and polarity of the charge. The resistivity of the propellant, which typically makes up more than 99% of the inhaled dose, is an important aspect for understanding the extent of charging in aerosols delivered by such devices [3]. Higher resistivities limit charge dissipation in the propellant, causing charge to accumulate [51]. Suspensions used in MDIs contain micron-sized drug particles suspended in the propellant, while in solution MDIs, the drug is dissolved in the propellant using a cosolvent. The main cosolvent in MDI formulations is ethanol to increase drug or excipient solubility [52]. A thorough understanding of these mechanisms requires systematically studying the materials and processes involved. Such an understanding may enable one to control the charge-to-mass ratio of the aerosol to achieve site-specific lung deposition of the active pharmaceutical ingredients (API).

Moreover, dielectric liquids suppress arcing and corona discharge and function as coolants and electrical insulators. Determining the resistivity permits one to identify and test the performance of such liquids when used in high-voltage applications, including transformers, capacitors, cables, and high-voltage switchgear [14]. Likewise, the widespread use of hermetic and semi-hermetic compressors in refrigeration has created a demand to verify the dielectric properties of the refrigerants used in these systems and to test potential alternatives where high resistivities are required [15]. As such, there is a demand for performing resistivity tests across a wide range of operating conditions. Unfortunately,

commercial resistivity cells currently only accommodate the needs of the power industry due to market demands and are designed to test the specific chemical profiles of the liquids used in this industry. This causes academics and researchers to develop their own cells when investigating the resistivity of alternative liquids, especially when said liquids require operating pressures outside of those of atmospheric conditions.

Some properties and the molecular structure of the aforementioned propellants are listed in Table 3.3.1. Several studies have been published previously by scientists to measure the resistivities of the propellants, with each study developing novel devices to perform the measurements.

Propellant	Molecular	Relative Density (kg/m3)		Viscosity (Pars)
ropenant	Structure Permittivity		25°C	
R134a	CH ₂ FCF ₃	1.15 - 1.22	1206.7	0.0005
R152a	CH_3CHF_2	1.004	899	0.00031
R227ea	CF ₃ CHFCF ₃	1.25 - 1.29	1590.6	0.00076

Table 3.3.1 Properties of the propellants	used in this study
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Values concerning the DC resistivity of R134a and R152a were first published by Fellows et al. [53] and later by Feja [41]. Fellows tested the resistivities using both AC and DC voltages and measured the DC resistivity for R134a and R152a to be 6.6 x $10^8 \Omega m$ and $2.2 \times 10^7 \Omega m$, respectively. Feja tested several electrical properties, including the relative permittivity, dielectric dissipation factor, and DC resistivity, across a temperature range between -30° C and 90° C, and tested mixtures with different concentrations of polyester oil. They found the DC resistivity of R134a and R152a to be $10^8 \Omega m$ and $10^7 \Omega m$, respectively. The resistivity of R134a was investigated by Meurer [15], followed by Dschung [39]. The latter also measured data for the resistivity of R227ea. Dschung [39] investigated the DC resistivity using a novel device, finding that R134a's and R227ea's resistivities were $6 \times 10^6 \Omega m$ and $1.3 \times 10^8 \Omega m$, respectively.
R152a possesses a global warming potential (GWP) substantially lower than the R134a and R227ea HFCs [54], [55]. Therefore, R152a is considered a potential candidate to replace the two HFCs (R134a and R227ea) in different applications, particularly under the strong impetus of the EU F-gas regulation and the 2016 Kigali Amendment of the Montreal Protocol to phase down the global use of high-GWP HFCs [56], [57]. Understanding the resistivity of R152a in relation to R134a and R227ea is, therefore, critical to further adopting R152a and determining its potential as an inhaler propellant. Moreover, R152a is a flammable substance; therefore, there is a risk of the propellant catching fire during the actuation of an inhaler if substantial charges develop, making it imperative that the resistivity is accurately determined to prevent such a scenario from occurring. Determining the volume resistivity of the propellants with mixtures of moisture and ethanol would also significantly help further our understanding of the properties of inhaler formulation and potentially improve them due to ethanol and moisture being widely used as cosolvents. The aim of this study is to design a novel resistivity cell capable of measuring high resistivities while ensuring the experimental process minimises contamination of samples to determine propellant resistivities with more precision and accuracy than previous studies. It is also to collect data on the propellants and their mixtures with ethanol and moisture with respect to their resistivity in the liquid phase at room temperature.

3.2 Charge Carrier Mobility

The charge carrier's mobility can be determined using the time-of-flight (ToF) method [44]. This is the time interval for the charge carriers to cross the interelectrode gap filled with the propellant. When a DC potential difference, V, is applied between the electrodes separated by a distance, L, the charge carriers will move in a uniform electric field, E, which is given by equation 34:

$$E = \frac{V}{L} \tag{34}$$

The propellants in liquid form under pressure behave as dielectric liquids. The charge carriers will be randomly distributed in the bulk of the liquid. When an external electric field stresses the liquid, the charge carriers will start moving across the electrode gap and manifest as electric current. This current can be measured using an electrometer connected in series with a liquid-filled gap. A single current peak will be registered if the dielectric liquid contains charge carriers with the same polarity. The magnitude of the drift velocity of the charge carriers, v, within the electrode gap, can be obtained as follows:

$$\nu = \frac{L}{t_{ToF}} \tag{35}$$

The drift velocity is also proportional to the field:

$$\mathbf{v} = \boldsymbol{\mu} \cdot \mathbf{E} \tag{36}$$

Where μ is the charge carrier mobility. Thus, μ can now be expressed by equation 36:

$$\mu = \frac{L^2}{t_{ToF} \cdot V} \tag{37}$$

where V is the applied potential.

Suppose the applied electric field is not strong enough to generate new charge carriers through ionisation or dissociation processes in the liquid or by injecting electrons from the cathode into the bulk liquid. In that case, the conduction current is defined by the movement of charge carriers that already

exist in the liquid, and the current will demonstrate Ohmic behaviour; the current, I, is proportional to V.

3.3 Design of the Resistivity Cell

3.3.1 Resistivity Cell

As it has been mentioned earlier cell constant is an important parameter to rely on when choosing size and dimensions of resistivity cell. Literature review revealed that cell with cell constant 0.113 m⁻¹, designed by Feja S. (see Table 2.2) allowed resistivity measurements of up to $10^{14} \Omega m$. Therefore, cell design based on cell constant 0.113 m⁻¹ is described below.

The resistivity cell consists of concentric cylinders enclosed by an outer stainless-steel housing with custom stainless-steel flanges mounted to both ends (see Error! Reference source not found.). EPDM (ethylene propylene diene monomer rubber) O-rings are installed between the flanges, outer housing, and measuring electrodes to form a hermetically sealed body. The electrodes are made of stainless steel. The measuring electrode is suspended between guard electrode cylinders at each axial end, with 1.5 mm-thick Sigma 500 polytetrafluoroethylene (PTFE) gaskets separating each of these cylinders. The outer housing diameter is 73 mm, the internal measuring electrode diameter is 44 mm, and the cathode diameter is 40 mm. There is a 2 mm separation between the cathode and the measuring electrode, along with the attached gasket and guard cylinders. The cathode has a 2 mm radius of curvature at each edge to limit field enhancement resulting from sharp edges. The length of the measuring electrode was determined to be 136 mm. This was to ensure a low enough cell constant to ensure our cell possesses a suitable resistivity measurement range when testing the desired HFCs. The measuring electrode is in contact with three ground contacts that radially alternate by 120° and are fed through fittings at the side of the housing. Three contacts are used to prevent misalignment of the measuring electrode, with only one of the contacts used for measurement. The inlet port consists of a threaded hole connected to the bottle containing the propellant and connected to a vacuum pump and nitrogen source. An outlet port at the top flange is also established to evacuate the fluids after each test. The cathode is connected

to the voltage source through a machine screw at the bottom of the cylinder and rests on a polyether ether ketone (PEEK) insulator. The guard electrodes at each side of the measuring electrode limit fringe fields so that current virtually only flows radially to improve measurement accuracy [45]. The outer housing exists primarily to ensure the firm positioning of the cylindrical electrodes. It also serves to improve safety by protecting the user from the electrodes and shielding the signal from stray electric fields external to the cell that may affect the measurement.

The electrodes are constructed from stainless steel 316 (SS316) and subjected to electro-polishing to ensure the metal in contact with the fluid possesses a smooth surface. Moreover, the calculations according to BS EN 13480-3:2017 suggest the design configuration is able to withstand a theoretical maximum working pressure of 9.08 MPa [46].



Figure 3.1 CAD drawings (2D) of resistivity cell components: (A) cross section of the complete resistivity cell and (B) internal components of the resistivity cell

3.3.2 Simulation of Electric Field within the Resistivity Cell

The electric field within the resistivity cell was calculated using a simplified model on the COMSOL Multiphysics (Version 5.4, Stockholm, Sweden) software with the finite element method. The simulation was used to determine the length of the guard electrodes when facing the cathode, at which the measuring volume would possess a homogenous electric field. The minimum length was determined to

minimise the volume of fluid required for each test and was found to be around 5 mm at each end of the measuring electrode. Another goal of the simulation was to calculate electric field distribution within the resistivity cell at the maximum field strength recommended by IEC 60247:2004, 250 kV/m [17]. Following boundary conditions were assigned to the model: 500 V was applied at the cathode while the other cell components, outside the fluid, were grounded. The model was meshed and solved for its electric potential distribution in the geometry. Poisson's equation for electrical potential (ϕ), denoted in equation 31, was solved with the potential difference across the electrodes as the boundary condition [47].

$$\nabla^2 \varphi = -\frac{\rho_f}{\varepsilon} \tag{38}$$

 ρ_f is the free charge density, assumed to be zero, and ε is the permittivity of the test fluid. The solution gave the potential distribution, which on differentiation provided the electric field distribution *E* according to equation 39:

$$\nabla \mathbf{E} = \frac{\rho}{\varepsilon} \tag{39}$$

The simulation was performed assuming that space charges were absent and the resistivity of the liquid was homogenous. Electric field distribution obtained from this simulation is presented on Figure 3.2. It clearly demonstrates that electrode geometry affects electric field at the corners of the cathode. With an average electric field inside the cell, which equals to 250 kV/m, electric field increases considerably to 600 kV/m at the curved corners due to increased charge concentration, which arises from weaker repulsion due to curved surface. The electric field homogeneity is significantly distorted at the bottom region between the electrodes and the EPDM seal as well as at the top of the cathode, as shown in **Error! Reference source not found.**(A) and **Error! Reference source not found.**(C), respectively. This

distortion might be explained by the presence of the seal, curved cathode corners and the different distances between measuring electrode and cathode in y and z directions. The importance of this simulation result comes from the fact that the high electric field strengths electrode curvature can lead to an early electrical breakdown during resistivity measurement and, therefore, it must be considered when performing the tests. This maximum field strength during a test may be higher in real life due to the possible formation of charge layers around the measuring electrode, which distort the field and affect the current flowing through the measuring electrode [32].



Figure 3.2 COMSOL simulations of the electrical field strength across the bottom (A), the whole cell (B) and at the top (C) of the anode. The plots depict 2D visualisations of the field strength in units of V/m, scaled with a factor of 10⁵ for better visibility. The electric field is homogenous (parallel field lines) within the measuring volume while being distorted (curved lines) at the edge regions on the

top and bottom

3.3.3 Experimental setup

3.3.3.1 Preparation of containers

The 500 ml whitey cylinders were pre-dried in a drying oven set at 102°C and left overnight to remove any contaminants, including moisture. They were then removed from the oven, set to one side, and allowed to cool. They were then fitted with a blank at one end and a ball valve at the other (so that long syringe needles could be inserted directly into the centre of the cylinder). They were then evacuated, filled with either 152a or 134a to 'condition' the metal surface with the existing moisture contained within the propellants, and left overnight in the lab at room temperature.

3.3.3.2 Preparation of dried ethanol

A molecular sieve (50g, 3 angstroms) was placed in a suitable container, connected to a 400 ml/min nitrogen purge, and put into an adapted drying oven. The oven was switched on, and the temperature was ramped up at 60°C per hour to 300°C to dry and activate the sieve. The oven was then switched off and allowed to cool. A bottle of absolute fresh ethanol was opened, and water content was predetermined via colorimetric titration (Karl Fischer titration) by injecting it into a Mitsubishi Chemical Analytech CA-310 moisture metre in accordance with ASTM-D1533[48]. A small amount of the activated sieve was added to an amber glass bottle and then filled with absolute ethanol. The bottle was then shaken by hand before being stored in a desiccator overnight in the lab. The moisture content of the ethanol was re-determined by injecting it again into the Karl Fisher apparatus. If the ethanol was not sufficiently dry, then more of the pre-dried molecular sieve was placed into another amber glass bottle, and the dried ethanol was decanted into the bottle and left in a desiccator overnight. The moisture content was then analysed using the Karl Fisher apparatus, and the clear liquid was decanted into a glass sample bottle fitted with a crimp-type septum. It was stored in a desiccator until needed.

3.3.3.3 Experimental setup

An image of the experimental setup is shown below (Error! Reference source not found.). A manometer in the form of a refrigerant gauge was connected to the top flange, as shown in Error! Reference source

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not found. The current was recorded every 0.1 seconds using a Keithley Electrometer model 6517B with a 10 atto amps (aA) current measurement resolution and a ± 0.2% accuracy at the 2 nA range. The electrometer was connected to a laptop with a custom LabVIEW program (Error! Reference source not found.) to run and record the results. The virtual instrument was designed to automate the data acquisition and allows one to observe the current against time in a graph format in real time to observe the performance. It allows one to adjust the settings, including the measurement delay and the number of measurements. The electrometer and voltage source was connected to the cell using crocodile clips, and 100 V was applied from the voltage source. The electrometer was connected to the LabVIEW (Version 2023 Q1, Austin, US) program on the laptop, and the current was measured over time.

3.3.4 Preparation of samples

3.3.4.1 Ethanol samples

The sample cylinder was evacuated, and a septum was added to the ball valve beneath a Swagelok nut. The required amount of ethanol was measured in an appropriately sized microlitre syringe, and the weight was recorded before injecting it into the cylinder through the septum and valve into the cylinder. The syringe was re-weighed, and the weight difference injected was recorded. The septum was detached, and the cylinder was plunged into liquid nitrogen for one minute. It was then weighed before attaching a 134a and 152a supply cylinder. The valves were opened, and liquified propellant was transferred into the cylinder. The sample cylinder was detached and re-weighed to determine the amount of 134a transferred. If the weight recorded was below the required amount, the transfer method was repeated until the correct amount of 134a had been deposited into the sample cylinder. The cylinder was put aside for four days to reach room temperature and to condition the metal surface again before analysing the contents for moisture.

3.3.4.2 Moisture samples

This preparation was similar to the procedure described above, with the exception that water was delivered into the cylinder via a microliter syringe with the liquefied propellant. If the moisture content

was below the levels calculated, the cylinder contents would be emptied, and the procedure would be repeated. The water concentration in this study is expressed as parts per million (ppm), defined with respect to the mass.

3.3.5 The methodology of performing the resistivity tests

To calculate the resistivity, a voltage of 100 V DC was applied to the 2-mm gap for 10- and 60-minute intervals, leading to an average field strength of about 50 kV/m, which was calculated using this equation $E = V/d_{d'}$ where V is applied potential and d is size of the gap , with the final current being used after a steady state had been achieved, indicating that the charge carriers have reached dynamic equilibrium. A voltage of 100 V was applied due to limited equipment availability, safety concerns, and to comply with the IEC standards. Initially, the current was measured for 10-minute intervals before increasing the interval to an hour. The HFCs were also investigated at commercial-grade purity, with >99.9% for R134a, R227ea, and R152a. However, it should be noted that these propellants are hygroscopic, and both commercial and pharmaceutical-grade samples may contain about 10 ppm of moisture. The procedure used involved purging the cell with nitrogen before vacuum pumping the cell with an ultimate vacuum pressure of 6 Pa (4.5×10^{-2} Torr) and then inserting the liquid propellant. The measured values allow one to easily discern whether the propellant is in its gaseous or liquid state, as they differ by orders of magnitude experimental setup described in Section 3.2.3.3 was used to measure electric current during experiments. Measurements were then repeated five times for each propellant at each time interval and three times for each moisture and ethanol concentration. The methodology for performing the tests is outlined as follows:

A transfer cylinder (500 ml) was filled to its maximum safe volume (400 ml) with propellant. The transfer cylinder was evacuated with a vacuum pump before filling. Then the cylinder was briefly chilled in liquid nitrogen to cool, using thermal gloves and goggles. The transfer cylinder was then filled from a larger cylinder before weighing it. The cell was then purged with nitrogen gas for 10 minutes, which helped to

remove moisture and oxygen. The cell was then evacuated with a vacuum pump for 30 minutes using 10^{-2} Torr pressure. The transfer cylinder was then placed in a water bath at 29 °C. It was left to acclimatise for between 30 and 60 minutes. An earth strap was attached to the cylinder and then filled with at least 50 ml of propellant from the transfer cylinder via the bottom fitting until the pressure exceeded the saturation vapour pressure.

A scale was used to determine the volume being filled. The pressure and temperature were measured from the refrigerant gauge, and the cell wall temperature was noted down using a RS pro 206-3722 temperature sensor. The final current measurement value was used to calculate the resistivity; after the initial peak, the current decayed and reached a steady state where the charge carriers reached dynamic equilibrium. The tests were measured and repeated at least three times at room temperature (21 - 23 °C) and various humidities in the lab. Temperature of propellants was kept as close as possible to the room temperature, where it was possible. The average temperature of R134a during the measurement was 15,1°C (17,2°C) for the 10 min (1 hour) interval, respectively. For 152a it was 26,7°C (23,6°C) for 10 min (1 hour), and for R227ea it was 16,1°C (17,4°C) for 10 min (1 hour), respectively.

The propellant was then evacuated into a ventilated fume hood. The device was enclosed in a grounded metallic cage that served as a Faraday cage to prevent electromagnetic fields from affecting the results. It also helped to protect the user from experiencing an electric shock during the experiment in the event of accidentally touching the electrified pipe at the bottom that connects to the anode. The cage was set up so that the power source turns off if it is opened while the voltage is on. The propellant mixtures with ethanol and water were also tested in the same way, with the mixtures tested in order of smallest concentration of ethanol (134a: 0, 0.1, 0.3, 0.96, 3.8, 7.2, 12.5%; 152a: 0, 0.1, 0.3, 1, 3.9, 6.1%) or water (134a: 46, 174, 250, 500ppm; 152a: 50, 277, 448, 896ppm) to highest. Before testing each concentration, the cell was purged with nitrogen, and the vacuum pump was used to empty the cell.



Figure 3.3 (A) The experimental setup of the resistivity measurement system and associated equipment, (B) Resistivity cell, and (C) protective cage enclosing the resistivity cell



Figure 3.4 Custom LabVIEW virtual instrument developed to program electrometer and record measurements. The current is measured as a function of time and displayed in a graph, the measurement delay and time period parameters can be adjusted

3.4 Results and discussion

3.4.1 The resistivity of pure propellants

The electrical resistivity was determined for three of the most widely used substitutes for CFC and HCFC propellants. After the DC voltage was applied, the recorded current decreased after an initial spike due to polarization effects. Transient charge-carrier drift processes occur due to ions being attracted to or repelled from electrodes based on their polarity. Figure 3.5 (A), (B) and (C) show the recorded current plotted as a function of time in the case of each propellant for a set temperature (~20°C). The first peak occurs after a few ms when the charge carriers in the dielectric liquid migrate from one electrode to the other. This duration is known as the time of flight (ToF).

Our preliminary tests have shown that the transit time for our dielectric liquids is 10 min and that extended stress, i.e. applied voltage, does not lead to significant further change in the current value, since the new equilibrium was reached. The tests are labelled by the order in which they were performed. It can be seen that the current values measured tend to decrease slightly as the order of the tests increases. This may be because the cell gets flushed with each test with the propellant, and some impurities get removed, leading to measured smaller current values. The measurements were repeated at least five times. Similar diagrams are observed for each of the propellants. The graphs tended to peak with a few hundred nA, with R134a tests peaking at higher currents when the voltage source was switched on at around 2000 nA before stabilising at approximately 50 nA. The R134a tests peaking at higher current values may be because these tests were conducted earlier than the other propellants; therefore, contaminant concentrations may have been slightly higher and settle at slightly higher current values after 10 minutes. It may be wise to repeat the tests more times until the readings stabilise and discard initial tests results due to contaminant fears to attain more reliable results.

The ToF, is determined from the time interval between when the voltage is applied first to the moment of the peak current. The value obtained for all three pure propellants is 1ms, limited by the time resolution of the current measurement. The charge carrier mobility is then calculated as $\mu = \frac{L^2}{t_{ToF} \cdot V} = \frac{2mm^2}{1ms \cdot 100V} = 4 \cdot 10^{-5} \frac{m^2}{Vs}$. And the drift velocity of the pure propellants is $v = \mu \cdot E = 2\frac{m}{s}$, with a

significant uncertainty of at least 50%.



Figure 3.5 Graphs showing the change in current over time for each of the propellants for each test that is completed, including (A) R134a, (B) R227ea, and (C) R152a. The average room temperature for these measurements was about 20°C

3.4.2 Resistivity for different measuring intervals

As it was mentioned earlier dielectric liquids are characterized by transient and steady states after voltage has been applied. At the transient state the number of charge carriers is still increasing. Therefore, resistivity measured during that state will not reflect the true resistivity of a dielectric liquid. But the resistivity measured during the steady state, which in our case has been reached after 10 minutes of applied voltage, will be representative of its true value, since the maximum number of charge carriers will be already created at that stage. But, in order to be sure that resistivity doesn't change with time additional measurements after 1 hour of applied voltage were performed. Results are presented on Figure 3.6, which demonstrates the differences between the resistivity values for different measuring times and various types of propellants. It can be seen that the resistivity for the 10-minute values tends to be significantly greater than the one-hour values; this is due to the number of charged particles increasing thereby leading to a downward drift in resistivity. The likeliest mechanism for this is the fate of the charge carriers produced early in the reading is not to disappear once discharged, but to leave some residual fragments that can add to the pool of potential charge carriers, so that the pool of charge carriers keeps increasing with time in the run. This was, however, not the case for the 152a propellant, which demonstrated the opposite relationship, with the 1-hour average value for resistivity being slightly larger. Here additional charge carriers are not being created after the original ones discharge at the electrodes. Instead, the pool of carriers remains roughly constant, with a slight reduction through the run leading to slightly rising resistivity. This could be accounted for by either the carriers surviving discharge to 'go around and do it again' as a semi-stable population (i.e. an initial positively charged carrier goes to the cathode, and picks up two electrons thus becoming a negatively charged carrier, goes to the anode, loses two and so on) or being discharged and lost from the carrier population to be replenished by an ionisation process (e.g. the ionisation of water) maintaining a pseudo-constant population. The 227ea and 134a were found to have a resistivity at least one order of magnitude higher than 152a. This is expected to result from the chemical structure of 152a being $C_2H_4F_2$. where a strong attraction exists between water molecules and the two fluorine atoms due to the high

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electronegativity of fluorine. When C₂H₄F₂ interacts with water, the highly electronegative fluorine atoms attract the partial positive charges on the hydrogen atoms of water molecules, leading to strong dipole-dipole interactions. This makes the 152a much more susceptible to water contamination. Resistivity dependence from temperature wasn't explored due to the lack of such dependence found in previous studies [39-41].

The tests were repeated at least three times due to the limited number of samples available. The resulting values of the resistivity for pure R134a, R227ea, and R152a, defined as the mean of the 10-minute interval measurements, after liquid reached steady state following the application of voltage step, are $(3.02 \pm 0.18) \cdot 10^{10} \Omega m$, $(1.31 \pm 0.08) \cdot 10^{10} \Omega m$, and $(2.37 \pm 0.4) \cdot 10^{9} \Omega m$, respectively. The uncertainties quoted are the standard deviations from the set of measurements taken.

Several small instrumental uncertainties limit the measurement. There is a 0.2% uncertainty in the current measured by the electrometer; the cell constant has an assumed uncertainty of 0.5%; and the applied voltage value has an uncertainty of 1%. Using Gaussian error propagation, the resistivity has a total instrumental uncertainty of about 1.1%. This is smaller than the standard deviations quoted above; the measurement is, therefore, not dominated by instrumental uncertainties.



10min VS 1h Pure Refrigerant Resistivity

Figure 3.6 Bar graph showing the mean resistivity values for each of the pure propellants measured at 10-minute and 1-hour intervals. The average temperature for the measurement of R134a was 15,1°C (17,2°C) for the 10 min (1 hour) interval, respectively. For 152a it was 26,7°C (23,6°C) for 10 min (1 hour), and for R227ea it was 16,1°C (17,4°C) for 10 min (1 hour), respectively. The average room humidity for the measurement with R134a was 39,1% (40,7%) for 10 min (1 hour), for R152a it was 29,0% (31,4%) for 10 min (1 hour), and for R227ea it was 44% (41%) for 10 min (1 hour)

3.4.3 Comparison of measured resistivity to other published results

Table 3.3.2 compares the results to data from other published literature. Feja⁹ analysed liquid R134a at varying temperatures. His results indicate that the resistivity of R134a is temperature-independent and in the order of $10^8 \Omega$ m. However, our measured values are on the order of $10^{10} \Omega$ m for ambient temperatures and saturation pressures for liquid phase measurements. A similar trend is observed when comparing the results to those obtained by Fellows et al.⁸. The measurements for R152a, which were performed to serve as a reference, correspond well to existing data. However, the measured value of the DC resistivity for R134a is about a factor of 45 higher.

One should mentioned that higher resistivity values point towards the improved level of sample purity, which in our case is \geq 99.9%. As it is highly dependent on the water content and other impurities of the tested substance and the value of the applied field strength, deviations are not unusual. The maximum water content present in our propellants, according to the manufacturer's specifications, is about 10 ppm. As described above, the measurement's uncertainties are assumed to contribute further to the detected deviations.

Maintaining the quality of the test fluid sample is very important because its electrical properties are susceptible to contamination and impurities. Samples for this study were prepared in a way to minimise moisture contamination. Also, a heat gun was used on the transfer cylinder, with its nuts loosened to evaporate and flush out any residual moisture, before the propellants were placed into the cell. Differences in the purity level of the test fluid sample is one of the reasons why it is complicated to compare measurements from various studies.

Table 3.3.2 The measured resistivity values $[Ohm \cdot m]$ obtained from the 10-minute intervals, compared to values quoted in other literature. The differences are discussed in the text

Propellant	This study	Fellows et al.	Feia [41]	Dschung [39]
		[53]	· • , • [· -]	2001018[00]
R134a	3.02 x 10 ¹⁰	6.6 x 10 ⁸	~10 ⁸	6.6 x 10 ⁶
R152a	2.37 x 10 ⁹	2.2 x 10 ⁹	~107	n/a
R227ea	1.31 x 10 ¹⁰	n/a	n/a	1.3 x 10 ⁸

Water content, for example, strongly influences the resistivity; the resistivity decreases when water is added. It can be visualised better by analysing eq. (4): Current depends on the number of charge carriers as: $I = n_q qAv_d$, where n_q is the number of charge carriers, q is their charge, A is a cross sectional area and v_d is their drift velocity. Substituting current in eq. (4) with above mentioned expression gives the dependence of resistivity from the number of charge carriers: $\rho = V/n_q qv_d L$. As it follows from this equation, resistivity is inversely proportional to the number of charge carriers, i.e. impurities in our case: the lower the number, the higher resistivity and vice versa. Given that our pharmaceutically graded samples had a very high level of purity, one could expect higher resistivity values for propellants. As it

was mentioned earlier the maximum water content present in our propellants, according to the manufacturer's specifications, is at most 10 ppm. This contamination is smaller than that of commercial-grade propellants used by Feja [41].

Let's look at the influence of resistivity on the accumulation and decay of charge in insulating liquid, since these processes play an important part in the safety of inhalers. Both charge accumulation, q_a , and charge decay, q_a , in propellants depend on resistivity as $q_a(t) = q_{max} \left[1 - e^{-t/\varepsilon \varepsilon_0 \rho} \right]$ and $q_d(t) = q_{max} e^{-t/\varepsilon \varepsilon_0 \rho}$, respectively with ε_0 being relative permittivity of free space. High values of resistivity make the term, $-t/\varepsilon \varepsilon_0 \rho$, in q_a a very small number, which is very close to 0, effectively turning $e^{-t/\varepsilon \varepsilon_0 \rho}$ to 1 and $q_a(t)$ to 0. Therefore, charge accumulation in liquid propellants with high resistivity will be very unlikely.

Additionally, differences in the experimental setup might have led to differences in measured resistivities as well. Feja used a modified cell arrangement according to IEC 60247 without guard ring [41]. The absence of a guard ring forced him to calibrate the test cell with a well-known liquid in advance. To summarise, several factors might explain discrepancies in resistivity values, found in the literature and obtained in the present study: The purity level of the test fluid sample directly influences electrical properties.. The improved and custom-designed cell used for this measurement is likely to contribute to a more accurate result than the one, found in the literature.

3.4.4 The resistivity of mixtures of propellants with water or ethanol

Fellows et al. [53] and Feja [41] studied the DC resistivity of pure R134a and R152a. However, this study presents further information regarding the resistivity of mixtures of propellants with moisture and ethanol.

Figure 3.6 shows the resistivity values for the R152a and R134a propellants with different water concentrations (R134a: 46, 174, 250, 500ppm; R152a: 50, 277, 448, 896ppm). Concentrations of water

and ethanol for measurements were defined by concentration ranges used in commercial MDIs by pharmaceutical companies. Moisture content will ionise in the electrical field, meaning the water molecules undergo electrolysis and split into hydrogen ions H^+ and hydroxide OH⁻. The hydrogen ions react with the water molecules at a low rate, forming hydronium ions, H_3O^+ . These charge carriers reduce the resistivity and will then respond with the electrons from the cathode and anode, forming dihydrogen H_2 and water H_2O and oxygen O_2 .

The values for R134a water concentrations can be seen to decrease exponentially in resistivity with increasing water concentrations before levelling off at 500ppm of moisture. There is an initial significant decline in resistivity between the pure propellant and the addition of 46ppm of moisture, resulting in order of magnitude decrease in resistivity. The graph for R152a and moisture shows a similar pattern with similar resistivity values for the different moisture concentrations, where the concentration of 900ppm of moisture showed a resistivity value that had plateaued relative to the 500ppm value. This plateau shows that added water concentrations may no longer significantly affect the resistivity of the mixture. This is because added water concentrations cause the resistivity to approach the value for water.

As has already been observed in Figure 3.6, 134a has about an order of magnitude higher resistivity than R152a, even at similar water concentration levels. This is understood to be related to the different ionic mobility. The dipole moments of the propellants are 2.06 Cm for R134a and 2.26 Cm for R152a, which means that R152a is a more powerful dipole. The HFC molecules cluster around the charged ions, but for R152a the ionic solvated cluster is smaller than that for R134a. This means that drag against the rest of the liquid medium as the ion moves in the cell field will be less, and the ionic velocity will be higher, leading to a higher cell current and lower resistivity for R152a.

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Figure 3.6 Graphs showing the resistivity values of R134a and R152a propellant mixtures with different concentrations of water: (A) R134a + water, (B) line graph of R134a + water, (C) R152a + water, and (D) line graph of R152a + water. The average room temperature for the set of measurements with R134a was 23,6°C, and the average room humidity was 39,7%. For the measurements taken with R152a, the average room temperature was 27,6°C, and the average room humidity was 42%

Figure 3.7 shows the resistivity values for the R152a and R134a propellants with different ethanol concentrations. Trace moisture can influence these studies, but due to the precautions taken, the moisture concentration is less than 10 ppm and, therefore, will have a negligible impact compared to the dominant effect of ethanol. It is expected that ethanol will be ionised in the electrical field via the reaction[58]:

$$CH_{3}CH_{2}OH \rightarrow CH_{3}CH_{2}O^{-} + H^{+}$$

and the hydrogen ion then instantly associates with non-ionised ethanol via:

 $H^+ + CH_3CH_2OH \rightarrow CH_3CH_2OH_2^+$

The two ions CH₃CH₂OH₂⁺ and CH₃CH₂O⁻ will lower the energy of the carried charge by virtue of the larger molecule, providing a considerable redistribution of the charge by polarising the bonds within the molecule. Ethanol charge dissipation is more potent than HFC solvation, meaning at low ethanol concentrations (less than 1%), the ions are surrounded by a much smaller HFC solvent cage, which is also more tenuously attached. But when ethanol concentration rises, a 'hybrid' solvation is formed, where both HFC and neutral ethanol molecules make up the solvation cage.



Figure 3.7 Graphs showing the resistivity values of R134a and R152a propellant mixtures with different concentrations of ethanol: (A) R134a + ethanol, (B) line graph of R134a + ethanol, (C) R152a + ethanol, and (D) line graph of R152a + ethanol. The average room temperature for the set of measurements with R134a was 24,5°C, and the average room humidity was 40,3%. For the

measurements taken with R152a, the average room temperature was 25,4°C and the average room humidity was 47%

Samples of propellants R134a and R152a with ethanol were prepared with slightly different concentrations due to the filling method, which didn't allow to set an exact concentration. As displayed in Figure 3.7, the resistivity drops with an increasingly large ethanol concentration. However, the resistivity plateaus at a concentration of approximately 4% and then slowly rises again. At ethanol levels below 4%, there is an increase in charge carriers, a slight decrease in cage sizes, and less drag on the HFA carrier medium, leading to an increase in current and a reduction in resistivity.

An explanation for the plateau and subsequent rise of resistivity for larger ethanol concentrations can be found by assuming that the rate at which negative ethanol ions are created slows down and is no longer proportional to the ethanol concentration.

Instead, hydrogen bonding will occur with an increased presence of ethanol molecules, both for neutral ethanol molecules and for ethanol ions. Hydrogen bonding [59] is a weak form of coupling between polar molecules; in this case, the partially negatively charged oxygen ion will bond with the partially positively charged hydrogen ion of another ethanol molecule. Hydrogen bonding is enhanced for the negatively charged ethanol ion CH₃CH₂O⁻ because the oxygen carries an even larger partial negative charge.

Consequently, larger clusters of charge carriers and a larger solvent cage are formed, and their ionic mobility and drift velocity drop; hence, this new dynamic state increases the resistivity of the propellant mixture. Further studies with varying temperatures and larger sample sizes should be conducted to more precisely estimate the concentration at which the plateau and turn-around effects occur.

The ToF for the mixtures was estimated as previously for the pure propellants by determining the time interval between when the voltage was switched on and when the peak current occurred. The current as a function of time was measured at least three times for each concentration value. However, the

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result is again limited by the time resolution of the measurement and was therefore again determined as 1ms, leading to the same drift velocities of $v = 2\frac{m}{s}$ with a considerable uncertainty of at least 50%.

In Figure 3.8, the measured resistivity graphs as a function of either the water or the ethanol concentration are superimposed for propellants R134a and R152a, indicating a similar behaviour for both materials. Knowing precisely how moisture and ethanol content influence resistivity can help improve medical inhaler formulations and increase their effectiveness. The resistivity of the propellant used in MDIs must be controlled and maintained at a fixed value; otherwise, an electrical charge will accumulate, which will prevent the uniform dissipation of the drug aerosol and limit the deposition of the pharmaceutical in the human lungs. More studies are needed to quantify the dependence of the electrical properties of propellants on a variety of conditions, for example, different temperatures and air humidity levels.

Furthermore, the studies performed with R152a are crucial to assessing its potential to be used as a propellant in MDIs, replacing R134a and R227ea in the future. The risk of being ignited during charge accumulation must be minimised, and therefore the resistivity properties of the pure substance and in mixture with water and ethanol have been extensively investigated.



Figure 3.8 Shows the change in resistivity for two different propellant mixtures with (A) different concentrations of water and (B) ethanol

3.4.5 Conclusion

In conclusion, the resistivity of propellants, including R134a, R152a, and R227ea, and their mixtures with different concentrations of ethanol and water were examined using a novel device developed for this study. The measured resistivity values for pure R134a, R227ea, and R152a were found to be 3.02×10^{10} Ω m, $1.31 \times 10^{10} \Omega$ m, and $2.37 \times 10^9 \Omega$ m, respectively. The resistivity values are generally higher than those quoted in the literature, which is attributed to several factors, such as higher purity, custom cell design, and an improved experimental process. The resistivity was also measured for mixtures of propellants R134a and R152a with different water and ethanol concentrations. It was observed that the resistivity dropped with increased moisture content. The dependence of the resistivity on the ethanol concentration was found particularly interesting. The measurements showed that adding ethanol caused a significant reduction in resistivity values for mixtures up to around 4% concentration, after which the resistivity values plateaued and even began to increase. This suggests that a specific concentration range of ethanol can significantly alter the electrical properties of these propellants. The reason for that is the formation of large molecule clusters and solvent cages that limit the mobility of charge carriers and thus increase the electrical resistivity.

The findings of this research can contribute to developing more efficient and effective propellants for various industrial applications, such as metered-dose inhalers. Precise knowledge and control of the resistivity can avoid charge effects, which would be detrimental to consistent lung deposition of drug aerosols. Future studies may investigate the effects of other additives and their concentration ranges on the resistivity of propellants to enhance their properties for specific applications. These measurements are experimentally very challenging. It is crucial to minimise the contamination of the samples with moisture, and the pressure in the cell must remain stable to ensure the propellants stay in liquid form, avoiding vapour formation. Therefore, improvements to the experimental setup should also be the subject of future studies.

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Chapter 4 Current Generated by Pharmaceutical Propellants using Novel Flow through Cell

4.1 Introduction

The past decades have seen significant advancements in the field of orally inhaled drug products, primarily focused on treating localised lung illnesses. Recently, this drug administration method has gained attention for its potential in systemic medication delivery, leveraging the lungs' expansive absorption area and minimal first-pass effects [98].

In the realm of inhalation drug products, in vitro testing plays a crucial role in understanding the properties and behaviour of these formulations before and during administration [99]. The effectiveness of orally inhaled drug formulations is intricately tied to the application of therapeutic devices like nebulisers, pressurised metered dose inhalers (pMDIs), and dry powder inhalers (DPIs). Each device is uniquely suited to deliver specific types of formulations. However, the challenges in this field are not just confined to the performance of these devices but also to the physicochemical characteristics of the formulations themselves [100].

Conventionally, the primary focus in developing orally inhaled drug products has been on ensuring the efficient delivery of active pharmaceutical ingredients from the device and their subsequent deposition in the human lungs. This is particularly challenging due to the small doses involved and the need for targeted delivery to specific regions within the lungs [101].

Given these challenges, the focus has shifted towards understanding the streaming current of metered dose inhaler (MDI) formulations in a flow-through cell. This novel approach aims to investigate how variables like flow rate, propellant type, and the materials of the inhaler influence the performance of pMDIs. This research is crucial for optimising pMDI designs, ensuring effective drug delivery, and improving patient outcomes [102].

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The flow-through cell apparatus, a critical tool in this research, offers several advantages. It allows for the modification of media types and flow rates within a single run, facilitates the determination of carry-over effects, and aids in correlating in vitro and in vivo studies. Moreover, the apparatus can simulate intra-luminal hydrodynamics more effectively compared to traditional in vitro setups [103]. The development of a reproducible testing technique for streaming current in MDI inhalers using the flow-through cell system is essential. This technique would not only aid in quality control studies of pMDIs but also enhance the prediction of their in vivo performance. In conclusion, the exploration of current generated in MDI formulations within a flow-through cell environment opens new avenues for optimising inhaler designs, paving the way for more effective and efficient pulmonary drug delivery systems.

4.2 Experimental Setup

This section outlines the experimental setup designed to investigate the triboelectrification and streaming current generated by the propellants flowing through a test tube at varying flow rates. Figure 4.1 presents schematic representation of the setup. The experiment utilizes the following components:

- a. Feed Cylinder: Houses the propellant supply.
- b. **Relaxation Cylinder/Chamber:** Allows pressure and temperature equilibration of the propellant before entering the test tube.
- c. Receiver Cylinder: Collects the propellant exiting the test tube.
- d. **Experimental/Test Tube:** Tube where current generated by propellant flowing across is measured across each end of the tube.
- e. Needle Valve: Valve used to regulate the propellant flow rate into the test tube.
- f. Ball Valves (Qty: 5): Control and isolate different sections of the setup.
- g. **3-way Ball Valve:** Facilitates direction switching of the propellant flow.
- h. Electrometer (KEITHLEY 6517B Electrometer): Measures the current generated by the fluid flow.
- i. Weighing Scale: Measures the propellant mass flow rate.

j. Vacuum Pump (Edwards xDS 5 dry scroll vacuum pump): used to vacuum system before

conducting each test.

- k. Liquid Nitrogen/Salt Ice: Provides cooling for the setup.
- I. Stopwatch: Measures the HFC-152A flow time.



Figure 4.1 Experimental setup.

All equipment connections strictly adhere to Figure 4.1. All equipment is securely fastened to prevent any breakage or slippage. The weighing scale and particularly the electrometer are calibrated beforehand to ensure measurement accuracy.

4.3 Experimental preparation

The experimental tube, chosen for its potential to be used within MDI inhalers, possesses an inner diameter of 2 mm. This tube serves as the conduit between the relaxation cylinder and the receiver cylinder. Both ends are cut cleanly using a sharp cutter. Olives and back nuts are then installed, ensuring cleanliness to prevent future leakage issues. Figure 4.2 illustrates the tube and olive components. Terminals (T1 and T2) are installed at both ends of the experimental tube, as shown in Figure 4.1. These terminals will connect to the electrometer via triaxial cables during the experiment, allowing measurement of both entry and exit currents. The experimental tube is then mounted vertically, with one end connected to the receiver cylinder and the other to the relaxation cylinder, as depicted in Figure 4.4.





Figure 4.2 Pneumatic tube along with the olive

Figure 4.3 : Edwards xDS 5 dry scroll vacuum pump

4.4 Feed Cylinder Preparation

The feed cylinder, with a capacity of 500 ml, will house the propellant. Due to safety considerations, a maximum volume of 400 ml is filled. The feed cylinder preparation involves the following steps:

a. Vacuuming: The Edward xDS 5 dry scroll vacuum pump (Figure 4.3) is connected to the feed cylinder to create a vacuum (ultimate vacuum ≈ 6x10⁻² mbar/4.5x10⁻² Torr). After 5 minutes, the feed cylinder valve is closed, and the pump is turned off.

- b. **Cooling:** The cylinder is placed in a cooling vessel, and liquid nitrogen is poured to cool it down. To maintain the temperature, the vessel is covered with metallic foil or any suitable insulator.
- c. **Propellant Filling:** Once cool, the weight of the cylinder is noted, and the scale is reset to zero. The feed cylinder is filled, in a vertical orientation from a supply cylinder. Utilizing a smaller cylinder and a hot-to-cold gravity transfer method facilitates faster filling. The filling continues until the weight reaches 400 grams.
- d. System Assembly and Vacuuming: The feed cylinder is installed in its designated vertical position (Figure 4.5). The complete assembly is connected to the vacuum pump (Figure 4.1), and valve v1 is opened to evacuate any remaining air. Careful attention is paid to all valve positions. After evacuation, the pump is turned off.
- e. **Vapor Balancing:** Valve v3 on the feed cylinder is slowly opened, allowing the vapor to gradually fill and balance the system. The increasing weight on the scale indicates this process. Once the weight stabilizes, it should show approximately a few grams (representing the vapor mass).
- f. Flow Rate Control: Control valve v6 (responsible for flow rate regulation) is closed, and the weight scale is zeroed.





Figure 4.4 : Close-up view of the experimental tube connections

Figure 4.5 : Feed cylinder's vertical mounting, ensuring utilisation of gravity for directing the propellant towards the experimental apparatus.

4.5 Electrometer preparation

This experiment utilizes a KEITHLEY 6517B electrometer, a highly refined DC multimeter offering greater precision and sensitivity than conventional counterparts. Its specialized input characteristics enable voltage, current, resistance, and charge measurements over a far wider range. In this instance, the electrometer is configured in picoammeter mode, allowing it to measure currents as low as 10 fA.

Furthermore, the use of triaxial cables minimizes noise in the electrical measurements. These cables feature dual layers of shielding (inner and outer) that effectively protect against electromagnetic interference (EMI), making them ideal for applications requiring superior signal integrity and reliability, such as medical imaging and specific electronic testing equipment. As shown in Figures 4.1 and 4.7, triaxial cables connect the electrometer to terminals T1 and T2 to measure the streaming current.



Figure 4.6 : Electrical connection of the electrometer to measure the streaming current

4.6 Measurements

With the setup primed, the experiment commences by opening the bottom valve (v7) of the feed cylinder (Figure 4.1). Propellant flows through the relaxation chamber and experimental tube under the sole influence of gravity, aided by the slight opening of the control valve (v6). This progressive transfer is reflected in the gradually increasing weight scale reading as the fluid enters the receiver cylinder. Simultaneously, electrical measurements are conducted via the electrometer connected across the experimental tube. The flow rate can be determined by recording the time taken for a specific mass of propellant to transfer (e.g. grams per minute).

Due to the influence of the relaxation chamber, the initial flow rate will likely differ from subsequent measurements throughout the experiment. While relying primarily on gravity, the control valve enables fine-tuning the flow rate to meet specific experimental requirements. The feed cylinder will be eventually empty, indicated by the pressure change in manometer and potential bubble formation in the experimental tube.

Finally, both the feed and receiver cylinder valves are closed. The receiver cylinder is weighed for reference, taking into account its empty, vacuumed, and cooled state. This experiment can be repeated with different cylinder capacities to gather more data for statistical analysis. For various combinations of valve stem materials and propellants the flow rate was measured once due to difficulties of creating the same flow rate for each valve stem material/propellant combination.



Figure 4.7: KEITHLEY 6517B Electrometer. Picoammeter mode is configured in this experiment

4.6.1 Key Considerations

a. Flow Rate: Ensure consistent flow rate across experiments by following a standardized valve

opening procedure:

 (i) Open the control valve (v6) to a designated number of turns. Record this number for reproducibility.

b. Data Acquisition:

- (i) Launch LabVIEW software.
- (ii) Start the stopwatch when the weight begins to increase. Allow approximately 1 minute for it to stabilize.

c. Flow Rate Calculation:

(i) Record the weight at 1-minute intervals for flow rate calculation.

4.7 Results and Discussion

This section begins with a thorough examination of the datasets obtained from the experiments, with the device illustrated in Figure 4.8. The data, highlighting its potential theoretical implications, is methodically organised. For ease of reference and detailed examination, the data pertaining to various propellants have been tabulated in Table 4.1, 4.2 and 4.3. This structured presentation facilitates an accessible and visual examination of the findings. Furthermore, to enhance understanding and aid in the interpretation of the results, additional graphical representations of the data are provided in the subsequent figures, Fig.4.9 – Fig. 4.15. For each parameter dependence of current from flow rate has been measured one time due to the complexity of flow rate control.

РОМ		РВТ		LDPE		VINYL				
Flow Rate	Current									
(gram/min)	(Amp)	(gram/min)	(Amp)	(gram/min)	(Amp)	(gram/min)	(Amp)			
153	1.7nA	102	16.2nA	27	233pA	31	873pA			
24	123pA	61	3.2nA	53	1.3nA	45	1.4nA			
52	681pA	36	1.6nA	74	4.1nA	98	3.1nA			
85	1.1nA	43	2.3nA	127	7.6nA	117	5.6nA			

Table 4. 1: Measurement of current as a function of flow rate and valve stem material for R152apropellant.R152a

Та	able 4. 2: Measurement of current as a function of flow rate and valve stem material for R227e	a
pr	opellant.	
	D 44 F	

K22/ea										
РОМ		PBT		LDPE		VINYL				
Flow Rate	Current									
(gram/min)	(Amp)	(gram/min)	(Amp)	(gram/min)	(Amp)	(gram/min)	(Amp)			
48	59pA	76	1.41nA	141	8.7nA	28	131pA			

71	2.57nA	129	2.2nA	46	653pA	36	257pA
164	6.8nA	45	868pA	21	81pA	77	785pA
125	4.7nA	104	1.8nA	78	3.6nA	94	1.3nA

Та	able 4. 3: Measurement of current as a function of flow rate and valve stem material for R134	la
pr	ropellant.	

K134a									
РОМ		РВТ		LDPE		VINYL			
Flow Rate	Current	Flow Rate	Current	Flow Rate	Current	Flow Rate	Current		
(gram/min)	(Amp)	(gram/min)	(Amp)	(gram/min)	(Amp)	(gram/min)	(Amp)		
27	386nA	31	683p A	42	1.2nA	43	383pA		
56	845nA	55	1.1nA	68	3.5nA	54	561pA		
74	1.4nA	97	1.7nA	91	4.7nA	102	1.3nA		
113	2.6nA	133	2.2nA	124	6.4nA	129	1.6nA		



Figure 4.8: Experimental apparatus employed to investigate the influence of valve stem material and propellant type on current generation in metered dose inhalers.



Figure 4.9: Current (amps) as a function of flow rate (g/min) for R152a propellant through different tube materials.


Figure 4.10: Current (amps) as a function of flow rate (g/min) for R134a propellant through different tube materials.



Figure 4.12: Flow rate dependence of current for propellants R152a, R227ea, and R134a through a Polyoxymethylene (POM) tube material.



Figure 4.11: Current (amps) as a function of flow rate (g/min) for R227ea propellant through different tube materials.



Figure 4.13: Flow rate dependence of current for propellants R152a, R227ea, and R134a through a Polybutylene terephthalate (PBT) tube material.



Figure 4.14: Flow rate dependence of current for propellants R152a, R227ea, and R134a through a Low-density polyethylene (LDPE) tube material.



Figure 4.15: Flow rate dependence of current for propellants R152a, R227ea, and R134a through a Vinyl tube material.

Analysis of the presented figures and tables suggests a general trend of increasing current with increasing propellant flow rate, regardless of the chosen valve stem material. This relationship likely arises from enhanced interaction between the propellant and the tube at higher velocities, leading to greater charge separation. Based on these observations, a statistically significant positive correlation between flow rate and current can be inferred. This implies that, across all materials except R227ea with LDPE and Vinyl stems, increasing flow rate results in a predictable and proportional increase in current. Further investigation with additional data points for R227ea using LDPE and Vinyl valve stems may be necessary to definitively establish a relationship or identify potential mitigating factors specific to this propellant-material combination.

Propellant Characteristics and Flow Dynamics: The figures show current (amps) as a function of flow rate (g/min) for different propellants through different valve stem materials. Distinct lines depict the observed trends for Polyoxymethylene (POM), Polybutylene terephthalate (PBT), Low-density polyethylene (LDPE), and Vinyl across the investigated flow range. They reveal the direct relationship between flow rate and current for the propellants suggests that increased flow velocity enhances charge separation and transport.

Material Properties and Triboelectric Effects: Although propellant flow rate establishes the overall trend of current, the choice of valve stem material also exerts some influence. This observation suggests significant differences in the triboelectric properties of the various materials and their respective interactions with the propellants. A detailed examination of Figures 4.9, 4.10 and 4.11 yields the following inferences.

- LDPE's High Currents: LDPE's tendency to generate higher currents could stem from its lower surface energy and higher tendency to hold onto electrons when interacting against the propellant. This triboelectric effect results in greater charge separation and higher currents.
- POM's Lower Currents: POM's smoother surface might reduce friction and charge separation, leading to lower currents. Its crystalline structure might also influence its electrical properties.
- PBT's Intermediate Behaviour: PBT's properties likely fall between those of LDPE and POM, resulting in moderate current levels.
- 4) **Vinyl's Minimal Current:** Vinyl's chemical composition and structure might inherently limit charge separation, causing its consistently low currents.

In addition to that, the roughness of valve stem surfaces likely plays a role, as increased roughness can promote charge separation. Furthermore, The strength of electrostatic interactions between propellant molecules and valve stem materials likely influences charge separation efficiency. However, experimental conditions like temperature, humidity, and the presence of other additives could also impact currents.

Statistical Analysis Of Measured Data.

While the observed trends in currents offer valuable insights, a rigorous statistical analysis is essential to confirm their statistical significance and quantify the influence of material and propellant variables. Engaging the power of statistical tests allows us to move beyond mere observation and establish statistically robust conclusions. In this particular study statistical analysis was performed by means of hypothesis testing. The

null hypothesis, H_0 , anticipates no relationships between parameters, while alternate hypothesis, H_a , predicts a relationship between parameters.

For that purpose we chose generalized linear model (GLM) to conduct statistical analysis of variables that might influence propellants current. The important advantage of this particular model lies in its inclusivity of various data types (numerical, categorical, etc.) as well as its ability to model non-linear relationships between variables by means of link function despite of its linear foundation. It will help us to determine whether observed differences in currents due to propellants type and due to valve stem materials are statistically significant or they have no relationships between them. A gamma regression model was constructed with log as a link function, $log(I) = \beta_0 + \beta_1 \cdot flow rate + \beta_2 \cdot valve material + \beta_3 \cdot$ propellant, positioning propellant, material, and flow rate as predictor variables for current. Table 4.4 presents results of the GLM analysis.

Coefficients	Variables	Estimate	Std. Error	t value	Pr(> t)
β_0		6.079695	0.276545	21.984	< 2e-16
β_1	Flow rate	0.021482	0.002308	9.308	1.46e-11
β_2	Material PBT	-0.253004	0.251137	-1.007	0.31978
	Material POM	-0.693016	0.246097	-2.816	0.00751
	Material Vinyl	-0.809608	0.245453	-3.298	0.00205
β_3	Propellant R152a	0.448649	0.217273	2.065	0.04546
	Propellant R227ea	-0.161055	0.212569	-0.758	0.45310

The rejection or acceptance of these null hypotheses is based on the p-values obtained from the GLM analysis. If the p-value is less than the chosen significance level (commonly 0.05), the null hypothesis is rejected, indicating that there is evidence to suggest a statistically significant effect. If the p-value is greater than the significance level, it indicates failure to reject the null hypothesis, suggesting that there is not enough evidence to conclude a significant effect.

In the context of the GLM analysis, there are multiple null hypotheses, one for each factor, are given below.

1) Null Hypothesis for Propellant:

H₀: There is no significant difference in mean current among the three propellants (R152a, R227ea, and R134a) when considering flow rate and material.

Alternative Hypothesis (H_a): At least one propellant has a significantly different mean current than the others.

2) Null Hypothesis for Material:

 H_0 : There is no significant difference in mean current among the four valve stem materials (POM, PBT, LDPE, and Vinyl) when considering flow rate and propellant.

Alternative Hypothesis (H_a): At least one material has a significantly different mean current than the others.

3) Null Hypothesis for Flow Rate:

 H_0 : There is no significant difference in mean current between different flow rates, regardless of propellant and material.

Alternative Hypothesis (H_a): Flow rate has a significant effect on mean current.

GLM results interpretation: Based on the provided statistics, let's analyse the effect of flow rate, propellants and valve stem material on current:

As it follows from Table 4.4, p value for flow rate is much smaller than 0.05 (p < 0.001). This indicates that flow rate has a strong impact on the current. For every unit increase in flow rate, the current increases by approximately 0.021 on the log scale.

With p = 0.32 PBT does not have a significant influence on current compared to the reference material LDPE. While for POM, p = 0.0075, and Vinyl, p = 0.002, with negative estimates, current is lower than for the reference material LDPE.

Compared to the reference propellant R134a, R152a, p = 0.045, has an effect on current, while R227ea,

p = 0.45, does not.

In order to choose the best valve material and the best propellant that generate the least current possible, we also performed estimated marginal means analysis, which is based on generalized linear model, described above. This analysis will demonstrate the average outcome for each category, which will be calibrated for other variables in the model. Results, presented in Table 4.5 and Table 4.6, include the difference between variables marginal means and a test that demonstrates whether this difference is statistically significant.

Contrasts	Estimate	Standard error	Degrees of freedom	t-ratio	p-value
LDPE - PBT	0.253	0.251	40	1.007	0.7460
LDPE - POM	0.693	0.246	40	2.816	0.0363
LDPE - VINYL	0.810	0.245	40	3.298	0.0106
PBT - POM	0.440	0.252	40	1.745	0.3144
PBT - VINYL	0.557	0.251	40	2.216	0.1363

Table 4.5. Estimated marginal means results for pairwise valve materials comparisons.

POM - VINYL	0.117	0.247	40	0.472	0.9647

Contrast	Estimate	Standard error	Degrees of freedom	t-ratio	p-value
R134a – R152a	-0.449	0.217	40	-2.065	0.1102
R134a – R227ea	0.161	0.213	40	0.758	0.7308
R152a – R227ea	0.610	0.218	40	2.797	0.0211

 Table 4.6. Estimated marginal means results for pairwise propellant comparisons.

LDPE generates higher current than both POM and Vinyl, with p = 0.0363 and p = 0.0106, respectively. The differences between LDPE and PBT are not statistically significant, p = 0.7460, implying that these materials perform similarly in terms of current generation. POM and Vinyl perform better, but the differences are not statistically significant. POM and Vinyl do not have statistically significant differences in their effects on current generation, p = 0.9647. Judging from this analysis POM and Vinyl stand out as the best-performing materials, particularly when compared to LDPE, as they generate lower current.

The estimated difference between R134a and R152a is -0.449 on the log scale, implying that R134a has a lower log current than R152a. The p-value is 0.1102, so this difference is not statistically significant at the 0.05 level as well as the difference between R134a and R227ea with p value of 0.7308. While the estimated difference between R152a and R227ea is 0.610, with a p-value of 0.0211 indicating statistical significance. That implies that R152a produces much higher current on the log scale, than R227ea.

Our experiments, which focused on the propellants R152a, R227ea, and R134a, and valve stem materials such as POM, PBT, LDPE, and Vinyl, demonstrated nuanced interactions affecting current generation. The distinct electrical properties of these materials, influenced by factors such as surface energy and electron affinity, play a crucial role in charge accumulation and dissipation. For instance, the disparity in current generation between Vinyl and LDPE highlights how material composition can significantly influence the outcome.

The ability of a material to conduct electricity is critical in determining how it accumulates or dissipates charge. Materials with higher conductivity allow charges to move more freely, leading to a quicker dissipation of accumulated charge. In contrast, insulating materials tend to hold onto their charge for longer periods. Given the electrical conductivities of POM (~10⁻¹² S/m), LDPE (~10⁻¹⁴ S/m), PBT (~10⁻¹³ S/m), and Vinyl (~10⁻¹² S/m) (at temperature 20-25°C), we can infer their impact on the current generation in the experiments. The very low conductivity of these materials, indicating their insulating nature, aligns with the observed low current generation. Specifically, LDPE, with the lowest conductivity, would be expected to exhibit the least current generation due to its higher resistance to charge flow. Conversely, POM and Vinyl, with slightly higher conductivities, would be expected show marginally higher current generation. However, the electrical conductivity values of the materials don't directly correlate with the current generation observed in the experiments. This discrepancy suggests that factors other than just material conductivity significantly influence the current generation in the setup. Additional variables like surface texture, chemical composition, or even the interaction dynamics between the propellant and the material, could be impacting the triboelectric effect and resulting current generation. This complexity underlines the multifaceted nature of current generation in MDI systems and the need for a comprehensive approach to understand it fully.

The behaviour of charged particles in the propellant, as they flow through the tube, is significantly influenced by electrostatic forces. These forces arise due to the interaction between the electrical field of the charged particles and the tube's surface. Depending on the material's electrical properties, this can either enhance or diminish the overall charge of the propellant. For example, a material with a higher electron affinity may attract more electrons, leading to a higher negative charge on the particle surface. Electron affinity refers to the energy change when an electron is attached to a neutral atom or molecule to form a negative ion. While electrical conductivity focuses on the movement of electrons within a material, electron affinity is a property of individual atoms or molecules. Unfortunately, finding reliable electron affinity values for polymers like POM, LDPE, PBT, and Vinyl can be challenging because polymers are large molecules with variable structures, determining a single electron affinity value for the entire polymer might not be accurate, as different segments of the polymer chain could have different affinities.

The relationship between flow rate and current generation is notable. This trend is consistent across all materials, suggesting a fundamental fluid dynamic principle at play. As the flow rate increases, the frequency of collisions between the particles and the tube's interior surface rises. This leads to more opportunities for charge transfer. A higher flow rate also means a faster movement of particles, which can enhance the kinetic energy of the particles and contribute to more effective charge separation.

The triboelectric effect is a phenomenon where materials gain or lose electrons when they come into contact with another material. In polymers like POM and LDPE, this effect is influenced by their molecular structure and surface properties. For instance, a rougher surface in POM may generate more static electricity due to increased contact area, leading to more charge accumulation. In contrast, LDPE's typically smoother surface might result in less static build-up. It is evident from the results that the triboelectric behaviours of POM, LDPE, PBT, and Vinyl, as influenced by their molecular structures and surface properties, show distinct variations in current generation under different conditions. While the general properties of these materials provide a theoretical basis for predicting their triboelectric tendencies, the experimental data suggests a more complex interaction between these materials and the propellants. The processing and manufacturing of materials like POM and LDPE also significantly influence their triboelectric properties. During production, factors such as the cooling rate, pressure applied, and the presence of additives can affect the surface texture and molecular alignment of these polymers. For example, faster cooling might lead to a rougher surface on POM, increasing its triboelectric potential by enhancing the contact area. Similarly, the incorporation of certain additives in LDPE could alter its surface smoothness, impacting its ability to accumulate or transfer charge. These manufacturing variations could account for the differing levels of static electricity generation observed in the experiment.

Hussein et al. (2023) found the electrical resistivity each of the propellants R134a, R152a, and R227ea [104]. The varying resistivity values for these propellants could explain the differences in current generation observed in the experiment with different propellants. A propellant with higher resistivity, such as R134a,

may lead to less charge transfer compared to a propellant with lower resistivity like R152a. This could account for the variations in current generation with each propellant type. The results, however, show a complex interaction between the propellants and the valve stem materials. The results don't follow a straightforward pattern based on these resistivities. This suggests that other factors, such as material-propellant interactions or specific surface properties of the materials, significantly influence the current generation in the experiment.

The data offers important insights for optimising MDI inhalers, especially in reducing aerosol charge for improved lung deposition. The experiment indicates certain materials generate less charge with specific propellants, suggesting their suitability for MDI valves. Based on the results, PBT and Vinyl are ideal materials when using propellant R134a especially at flow rates higher than 80g/min while flow rates between 30 – 80 g/min POM is also a suitable candidate, as they generate lower charge, which is beneficial for drug deposition in the lungs. For propellant R152a, POM and Vinyl are preferable, especially above 60g/min, while LDPE may be considered if utilising flow rates below 60g/min due to their reduced charge generation. Similarly, with R227ea, Vinyl and PBT at flow rates above 60g/min, show optimal properties with less current recorded. Selecting these material-propellant combinations can lead to a significant reduction in aerosol charge, enhancing the efficiency of MDIs in delivering medication to the lungs. The study also highlights the impact of flow rates on charge generation. Lower flow rates generally result in reduced charge, beneficial for enhancing drug deposition in the lungs. This information can guide the selection of valve stem materials and flow rate settings in MDI designs, aiming to minimise charge and maximise drug delivery efficiency.

4.7.1 Conclusion

The investigation into currents in MDI systems reveals distinct influences of various factors. Primarily, the flow rate emerges as a critical determinant, exhibiting a robust and statistically significant effect on the current generation where the rate of flow directly correlates with the subsequent generation of current. The type of propellant and the valve stem material also demonstrate an impact but it is more nuanced. Generated current depends on the stem valve material-propellant combination which has been confirmed

by statistical analysis. The combination POM-R152a exhibits the lowest current even at high enough flow rates, while Vinyl is a good choice of the valve stem material for R227ea and R134a propellants. The composition of both stem valve and propellant might play a significant role on their interaction during the flow. Further, more detailed investigation of that interaction could reveal the mechanism understanding of which would allow to build more efficient and safe inhalators.

Chapter 5 Major Conclusions and Future Works

5.1 Introduction

This chapter concludes and summarises the key findings from the exploration of the electrostatic properties of MDI inhaler formulations. The study provides recommendations for further research in the pharmaceutical industry, proposing innovative solutions to mitigate the knowledge gap and limitations associated with conventional measurement methods, by designing and developing customised resistivity cells and flow-through devices for both academic and industrial applications.

5.2 Research Overview

Effective delivery of pharmaceutical medications, such as the use of metered dose inhalers (MDIs) to deposit drugs into the human lungs, is highly dependent on drug formulation, design of delivery device, and physiochemical properties of the aerosols produced after actuation. Over the years, there has been a tremendous advancement and engineering of delivery devices to achieve effective deposition of drug aerosol to the human lungs, however, regulatory demands and effective deposition are yet to be satisfied. The transition of propellant type from chlorofluorocarbons (CFCs) to hydrofluoroalkanes (HFAs) to mitigate the harmful impact of its emissions to the ozone layer has been established. To satisfy further climate change demands, HFA-152a propellant was developed to reduce the emission level of drug formulations used in MDIs, although, the electrostatic properties of this newly developed formulation are yet to be explored.

This research has contributed to the existing body of knowledge through its comprehensive investigation into the electrical volume resistivity of dielectric liquids over various operating conditions. Researchers are forced to design and develop custom devices for a particular set of test conditions as a result of narrow operating pressure ranges of commercial offerings. It has also addressed key gaps identified in the literature review in Chapter 2, including the discrepancies between operating pressures in commercial cells and cells designed for academic purposes, and the need for a standardised method to mitigate moisture content when conducting resistivity tests. In the same chapter, the study also provided insights on the comparison among various works conducted on cell design for resistivity tests, while recommendations were stated to ensure effective design of future resistivity cells. Furthermore, the behaviour of charge carriers and their corresponding mobility in dielectric liquids were also detailed. A comprehensive explanation of the difference between AC and DC resistivity measurement was also given in the study.

The research progressively stretches the knowledge of theoretical models and governing principles involved in the study of electrostatic properties, focusing on the fundamental factors such as formulation characteristics, material selection and design. Therefore, the work supports the reproducibility of experimental outcomes to an appreciable level. In addition, the investigation into MDI formulations improves practical understanding of electrostatic impacts on drug delivery, addressing key gaps in the literature.

Chapter 3 of the study presented a methodology to design and fabricate a resistivity cell which was set up to conduct experimental procedures for the liquid resistivity of dielectric liquids. Initially, the electric field strength within the resistivity cell was modelled and designed computationally using COMSOL 5.2 software, establishing boundary conditions to simulate the behaviour of the dielectric liquid during operation. Afterwards, fabrication of the modelled cell was achieved with the design configuration able to withstand a theoretical maximum working pressure of 9.08 MPa. The experiment of the study considered propellants used as refrigerants and MDI propellants such as Tetrafluoroethane - $C_2H_2F_4$ (R134a), Difluoroethane, $C_2H_4F_2$ (R152a), and Heptafluropropane, CF_3CFHCF_3 (R227ea), and their corresponding mixtures at differing concentrations of ethanol and moisture. In the liquid phase, the DC volume resistivity was measured using a novel concentric cylinder-type capacitance cell designed in-house. The resistivity was measured using a novel concentric cylinder-type capacitance cell designed in-house. The resistivity for the propellants (R134a, R152a, and R227ea) was found to be $3.02 \times 10^{10} \Omega m$, $2.37 \times 10^9 \Omega m$ and $1.31 \times 10^{10} \Omega m$, respectively. The electrical resistivity data obtained was found to be at least two orders of magnitude higher than the limited data available in the literature. The resistivity of propellant mixtures containing moisture concentrations ranging from 5 to 500 ppm and ethanol concentrations ranging between 1000 and 125,000

ppm was determined. The resistivity was tested across 10-minute and 1-hour periods and was performed in accordance with the contemporary IEC 60247 standard.

5.3 Significance of Research Study

The research possesses importance in furthering the field of medical respiratory research by focusing on the understudied aspect of electrostatic properties in metered dose inhalers (MDIs). A thorough investigation of the inherent interplay between fluid dynamics, formulation characteristics, and charging mechanisms involved in generating aerosols, aims to evaluate the complexities associated with electrostatic charge on inhaled particles. With the understanding of the influence of varying formulation concentrations and fluid flow parameters on the electrostatic properties of MDIs, the research is positioned to optimise MDI design for predetermined drug delivery rates with the consideration to mitigate oropharyngeal discomfort. Overall, the study shows the potential to improve the precision and efficiency of MDIs, progressing the path for targeted lung deposition of therapeutic substances, thereby enhancing treatment solutions and patient experiences in respiratory care.

5.4 Contribution to Knowledge in the Field

This study primarily offers critical contribution to the existing body of knowledge in medical respiratory research by systematically analysing the inherent relationship between electrostatic properties and the effective performance of metered dose inhalers (MDIs), The consideration of charging mechanisms when aerosols are generated and the thorough evaluation of streaming currents and zeta potentials offer a subtle understanding the synergic influence of formulation concentrations, ionic interactions, and fluid flow factors on the electrostatic characteristics of MDIs. The research also contributes to the advancement of theoretical models, placing more light on the dependence of streaming current on fluid flow dynamics, formulation properties, material choice and design, and introducing correction factors that account for the differences in theoretical findings and experimental outcomes. Consequently, the study promotes the reproducibility of experimental results to an appreciable extent. The optimisation of MDI design for particular drug delivery rates, in relation to the exploration of innovative solutions like modelling flow through resistivity cells

promises practical progress in inhalation-driven aerosols. In addition, the investigation into solution MDI formulations improves practical understanding of electrostatic impacts on drug delivery, addressing key gaps in the literature. Ultimately, the study significantly promotes the scientific understanding of electrostatic behaviour in MDIs, providing primary foundation for enhanced design of drug delivery devices, and more effective medical approach to pulmonary and respiratory care.

5.5 Impact of Research Outcome

Insights derived from the evaluation of electrostatic characteristics of metered dose inhalers, specifically, the charging mechanisms during aerosol generation, are positioned to form the foundation of scholarly articles in respiratory medicine and pharmaceutical science research, both in the United Kingdom and abroad. Moreover, the modelling of a typical MDI through the designed flow-through resistivity cell, a novel approach introduced in the study, showcases a valuable tool for studies beyond the current state in the field of engineering research. Its application spans across the immediate scope of MDIs, offering a flexible platform for investigating fluid flow characteristics, formulation properties, and their resultant influence on electrostatic phenomena in various engineering contexts. This innovative tool is anticipated to promote advancements in respiratory research in the United Kingdom and contribute to the broader understanding of aerosol delivery systems in medicine.

5.6 Key Findings

From the experimental results on the dependence of electrical resistivity of the propellant with respect to increasing moisture content, the resistivity values for R134a were observed to fall exponentially with increasing moisture content before levelling off at 500ppm of moisture content. Initially, there was a significant drop in resistivity between the pure propellant and the propellant mixture containing 46ppm of moisture, which amounted to a resistivity difference in order of magnitude. The resistivity-moisture content plot for R152a propellant showed a similar pattern with similar resistivity values for the different moisture concentrations, where the concentration of 900ppm of moisture showed a resistivity value that had

plateaued compared to the 500ppm value associated with the R134a propellant. Knowing precisely how moisture and ethanol content influence resistivity can help improve medical inhaler formulations and increase their effectiveness. The resistivity of the propellant used in MDIs must be controlled and maintained at a high as possible and a fixed value; otherwise, an electrical charge will accumulate, which will prevent the uniform dissipation of the drug aerosol and limit the deposition of the pharmaceutical in the human lungs. The main objectives of the study were achieved:

- The design and fabrication of a pressurised resistivity cell to study the electrical resistivity of HFA 134a,
 152a, and 227ea propellants were successfully carried out
- It was observed that the resistivity dropped with increased moisture content. The dependence of the resistivity on the ethanol concentration was found particularly interesting. The measurements showed that adding ethanol caused a significant reduction in resistivity values for mixtures up to around 4% concentration, after which the resistivity values plateaued and even began to increase. This suggests that a specific concentration range of ethanol can significantly alter the electrical properties of these propellants. The reason for that is the formation of large molecule clusters and solvent cages that limit the mobility of charge carriers and thus increase the electrical resistivity. An explanation for the plateau and subsequent rise of resistivity for larger ethanol concentrations can be found by assuming that the rate at which negative ethanol ions are created slows down and is no longer proportional to the ethanol concentration.

Similarly, a detailed analysis of the effects of different propellants (R152a, R227ea, and R134a) on current generation in MDI systems, considering various valve stem materials (POM, PBT, LDPE, and Vinyl). A general trend of increasing current with increasing propellant flow rate was observed, irrespective of the valve stem material used. The study also highlights significant differences in triboelectric properties among the materials, affecting their interactions with the propellants. The experimental results indicate that factors beyond material conductivity, like surface texture and chemical composition, influence the triboelectric

effect and resulting current generation. This suggests a complex interaction between propellants and materials, necessitating a comprehensive understanding of these factors for optimizing MDI design.

5.7 **Recommendations**

The outcome of the research prepares a pathway for further grounds and scope that can be covered. Therefore, future work in the following areas is recommended:

- Future studies may investigate the effects of other additives and their concentration ranges on the
 resistivity of propellants to enhance their properties for specific applications. These measurements are
 experimentally very challenging. It is crucial to minimise the contamination of the samples with
 moisture, and the pressure in the cell must remain stable to ensure the propellants stay in liquid form,
 avoiding vapour formation.
- More studies are needed to quantify the dependence of the electrical properties of propellants on a variety of conditions, for example, different temperatures and applied voltages.
- Further studies with larger sample sizes should be conducted to more precisely estimate the concentration at which the plateau and turn-around effects occur.
- Further analysis of material-propellant interactions should be conducted for the flow through set of experiments, in greater depth how different materials interact with various propellants, focusing on chemical and physical aspects of the interaction.
- Expanded range of materials and propellants should be tested for the flow-through experiment, with a broader range of materials and propellants to understand their triboelectric properties and effects on current generation more comprehensively.

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Chapter 7 Appendix

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Measurement of electrical resistivity of hydrofluorocarbons - A review

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A R T I C L E I N F O	A B S T R A C T
Keywords: Resistivity Refrigerant Hydrofluorocarbon Dielectric liquid	The expansion of applications involving hydrofluorocarbons has generated a demand for devices capable of measuring the electrical volume resistivity of such liquids across diverse operating conditions. The narrow operating range of commercial offerings, particularly in regard to pressure, compels researchers to develop custom cells for the desired test conditions. A review of resistivity cell designs developed over the past three decades is presented. Academic studies in the past have focussed on the development of cells for the purpose of testing the resistivity of refrigerants in liquid phase under high pressures. The fundamental principles underlying resistivity measurement are discussed while emphasis is placed on practical aspects of cell design. The review addresses facets including contemporary standards, limitations and constructional details of academic and commercial cells. It should serve as a guide for future researchers attempting to develop custom resistivity cells for the device liquids.

1. Introduction

The electrical volume resistivity of dielectric liquids is an important parameter that offers information on the insulating ability, purity and behaviour of a liquid in the presence of an electric field. Resolving the resistivity of dielectric liquids has therefore become an important requisite for multiple industrial applications. Dielectric liquids serve to suppress arcing and corona discharge as well as functioning as coolants and electrical insulators. Determining the resistivity permits one to identify and test the performance of such liquids when used in high voltage applications including transformers, capacitors, cables and high voltage switchgear [1]. Likewise, the widespread use of hermetic and semi-hermetic compressors in refrigeration has created a demand to verify the dielectric properties of the refrigerants used in these systems and to test potential alternatives where high resistivities are required [2]. More recently, identifying the resistivity of dielectric liquids has piqued the interest of the pharmaceutical industry where dielectric hydrofluorocarbons (HFCs) are widely used as propellants in metered dose inhalers. The resistivity of these propellants impacts the charge characteristics of the active pharmaceutical ingredients delivered to patients thereby affecting drug deposition in the lungs. Determining the resistivity of these HFCs is therefore critical to understand their suitability and effectiveness as inhaler propellants [3]. Besides, these applications constitute only a handful of examples where dielectric liquids are currently used. As such, there is a demand for performing resistivity tests across a wide range of operating conditions. Unfortunately, commercial resistivity cells, as of present, only accommodate the needs of the power industry due to market forces where they're designed to test the specific chemical profiles of the liquids used in this industry. These include a small number of oils comprising mineral, ester and silicone. This forces academics to develop their own cells when investigating the resistivity of alternative liquids, especially when said liquids require operating pressures outside that of atmospheric conditions. Herein a comprehensive review of studies and factors concerning resistivity cell design is presented.

2. Theory of electrical bulk resistivity

The volume resistivity of a dielectric liquid is the quotient of the applied electrical field strength and the current density [4]. It's an intrinsic property that measures a liquid's ability to resist the flow of electric current and depends on the test conditions when performing the measurement. A material with a high resistivity denotes the lack of free electrons, ions and ion forming particles as well as indicating the presence of a low concentration of electrically conductive contaminants. It can be used to analyse the deviation of a material from the desired dielectric characteristics [4]. It's represented by the symbol ρ with an SI unit of Ω m. Resistivity is equal to the reciprocal of the electrical conductivity σ , with the latter having an SI system unit of Siemens per metre

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OPEN Liquid resistivity of pharmaceutical propellants using novel resistivity cell

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Metered-dose inhalers employ propellants to produce pharmaceutical aerosols for treating respiratory conditions like asthma. In the liquid phase, the DC volume resistivity of pharmaceutical propellants including R134a, R152a, and R227ea, was studied at saturation pressures and room temperature (not vapour phase). These measurements are essential for industries like refrigerants. Aerosols from metered dose inhalers (MDIs) with these propellants become electrically charged, affecting medicament deposition in lung. The resistivity was measured using a novel concentric cylinder-type capacitance cell designed in-house. The resistivity for the propellants (R134a, R152a, and R227ea) was found to be $3.02 \times 10^{10} \Omega$ m, $2.37 \times 10^{9} \Omega$ m and $1.31 \times 10^{10} \Omega$ m, respectively. The electrical resistivity data obtained was found to be at least two orders of magnitude higher than the limited data available in the literature. Challenges in the resistivity cell's development and performance are discussed, with a focus on various propellants and their mixtures with ethanol and moisture concentrations. The resistivity of propellant mixtures containing moisture concentrations ranging from 5 to 500 ppm and ethanol concentrations ranging between 1000 and 125,000 ppm was determined. The resistivity was tested across 10-min and 1-h periods and was performed in accordance with the contemporary IEC 60247 standard.

R134a (Tetrafluoroethane-C2H2F4), R227ea (Heptafluropropane, CF3CFHCF3), and R152a (Difluoroethane, $C_2H_4F_2$) are hydrofluorocarbons (HFCs) widely used as propellants in the pharmaceutical industry for metered dose inhalers (MDI) to generate inhalable drug aerosols to treat respiratory conditions. Such HFCs were developed to the second secon oped to overcome environmental issues associated with the use of chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs), as the chlorine in those molecules is responsible for the depletion of the ozone layer. Besides their application in MDIs, they are also used as refrigerants^{1,2}. It has been recognised that when these inhalers deliver the aerosols, they become electrically charged. Consequently, the medicament deposition in the human lungs is also influenced by the level and polarity of the charge. The resistivity of the propellant, which typically makes up more than 99% of the inhaled dose, is an important aspect for understanding the extent of charging in aerosols delivered by such devices³. Higher resistivity limit charge dissipation in the propellant, causing charge to accumulate⁴. Suspensions used in MDIs contain micron-sized drug particles suspended in the propellant, while in solution MDIs, the drug is dissolved in the propellant using a cosolvent. The main co-solvent in MDI formulations is ethanol to increase drug or excipient solubility⁵. A thorough understanding of these mechanisms requires systematically studying the materials and processes involved. Such an understanding may enable one to control the charge-to-mass ratio of the aerosol to achieve site-specific lung deposition of the active pharmaceutical ingredients (API).

In addition, dielectric liquids play a vital role in suppressing arcing and corona discharge, while also serving as coolants and electrical insulators. The determination of resistivity allows for the evaluation and testing of the performance of these liquids in high-voltage applications, such as transformers, capacitors, cables, and high-voltage switchgear⁶. Similarly, the use of hermetic and semi-hermetic compressors in refrigeration has led to the need for verifying the dielectric properties of refrigerants employed in these systems and exploring alternative options that require high resistivity7. Consequently, there is a growing demand for conducting resistivity tests across various operating conditions. Regrettably, existing commercial resistivity cells are tailored solely to the requirements of the power industry, neglecting the diverse chemical compositions of liquids investigated outside this industry. This limitation prompts academics and researchers to develop their own cells specifically suited for studying the resistivity of alternative liquids, particularly those operating under non-atmospheric pressures.

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