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Pharmaceutical Aerosol: An Overview

Ms. Shilpa Shyam M [1], Dr. L V Vigneshwaran [2], Mohammed Rahees A [3], Mohammed Hashir M [4], Dr Ajith Babu T K [5]

[1]Department of Pharmaceutics: Assistant Professor, Malik Deenar College of Pharmacy, Kerala University of Health Science, Thrissur.
[2]Department of Pharmaceutics: Professor and HOD, Malik Deenar College of Pharmacy, Kerala University of Health Science, Thrissur.
[5]Department of Pharmaceutical Chemistry: Principal, Professor, Malik Deenar College of Pharmacy, Kerala University of Health Science, Thrissur.

ABSTRACT

The location and amount of medication that is deposited in the respiratory system affect how effective inhalation is in addition to the drugs themselves. This article looks at the main variables that affect how inhaled .The human lung is where aerosols are carried and deposited. It addresses the accumulation of aerosols in both healthy and sick lungs, primarily based on human research with non-imaging techniques. It also explores the effects of flow pattern on aerosol deposition. The relationship between the location of drug deposits in the lungs and their therapeutic effects when breathed is briefly discussed in the article. Studies show that the total amount of deposition in the lungs is not a good predictor of clinical efficacy.

KEYWORDS: Pharmaceutical aerosol , preformulation ,MDI , Propellent

INTRODUCTION

Pharmaceutical aerosols are goods with therapeutically active components that are compressed and released when the proper valve system is activated. This technique relies on pressurised air pressure to force the contents out of the container.

In 1950, medicinal aerosols began to be developed.They were designed to treat a variety of dermatological disorders, including minor wounds, burns, and infections.[1]

Although the name "aerosol" wasn't coined until recently, inhalation therapies and systems for treating medical diseases have been used for thousands of years,not until 1920. Inhalation treatment was employed by traditional cultures, such as Ayurvedic medicine in ancient India circa 2000 BCE, to treat respiratory ailments . Ancient Egyptians are known to have used the vapour of the herb Hyoscyamus muticus, which has anticholinergic qualities, for medicinal purposes.
Pine and eucalyptus essential oils were used in inhalation therapy by the Persian physician Ibn Sina, widely known as Avicenna, centuries ago to treat specific respiratory problems.

The product concentration, which contains the pharmaceutically active ingredient, and the propellant combine to generate the aerosol, which serves as a dose form. components, cosolvents, and any additional filler materials required to improve the stability and effectiveness of the product. The product concentrate can be dissolved in water, made into a semisol, or suspended, and then used to create aerosol systems, which can be pastes, emulsions, dry powders, solutions, or dispersions.

ADVANTAGES

• The affected area can receive direct delivery of the medication. Preventing the hydrolysis of medications is possible.

• Oral inhalation is one way to administer drugs.

• Medication application is simple.

• When there is no air, the product does not oxidise.

• Oral medications do not pass through the gastrointestinal tract. It has a lower likelihood of disintegrating as a result.

DISADVANTAGES

• Aerosol preparations are expensive.

• The cooling action of highly volatile propellants may induce discomfort on damaged skin; some propellants are quite poisonous.
• When a medicine is not soluble in propellant, many problems arise[2].

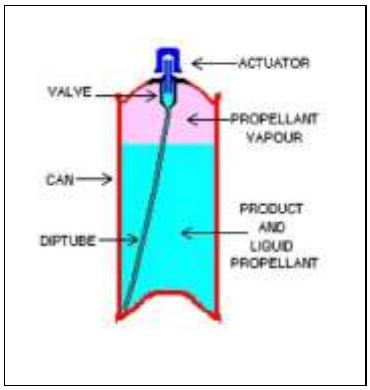

Fig 1:Parts of Aerosol

TYPES OF AEROSOLS[3,4]

Fine solid or liquid particles suspended in a gas, usually air, are known as inhalational aerosols. Nebulizers and inhalers are a few examples of inhalational aerosols. Inhalers are used to administer medication directly to the lungs in order to treat respiratory disorders such as COPD and asthma. Nebulizers and inhalers are similar in that they both use a mist to administer medication to the lungs.

Non-Inhalational Aerosols: Unlike inhalational aerosols, which are meant to be inhaled, non-inhalational aerosols are a suspension of fine solid or liquid particles in a gas. They are employed for air filtration, dust management, pressure application, coating surfaces, and more. Aerosols that are not inhaled include foams, sprays, dust-controlling agents, filters, etc.

Topical aerosols: An aerosol type created especially for application to the skin or other exterior surfaces is known as a topical aerosol. The goal of topical aerosols is to apply their active components topically. They are mostly used for sun protection, moisturising, disinfecting, pain treatment, and wound healing. Topical aerosols include, among others, hairspray, sunscreen, antibiotic, and lidocaine sprays.

Metered dose inhaler (MDI): An MDI is a portable medical device that mists a precise, predetermined dosage of medication into the lungs during use. They are used to treat allergies, COPD, and asthma, among other respiratory diseases.

An NMDI is a non-metered dosage inhaler. An NMDI is a device that administers medication directly to the lungs; in contrast to MDIs, it does not administer a dose that has been predetermined. The user's breathing technique and other factors may affect the amount of medication they receive. NMDI is available in a number of forms, including respimat, nebulizers, dry powder inhalers (DPI), and soft moist inhalers (SMI).

Two-phase aerosols: A system of two phases, a liquid phase and a vapour phase, that make up an aerosol. A liquefied propellant and the product concentration are dissolved or disseminated within the liquid phase. Evaporated propellant gas from the liquid phase makes up the vapour phase. Hair spray, deodorant, room freshener, and other products are examples of two phase aerosols.

Aerosols with three phases: An aerosol with three phases is made up of a liquid propellant phase, an aqueous product phase, and a vapour phase. Liquid propellant phase is made up of some product concentrate that has been dissolved or scattered in the liquefied propellant. The product concentration is dissolved or dispersed in water or another aqueous solution to form the aqueous product phase, which is a separate liquid layer. Propeller gas that has evaporated from the liquid propellant phase makes up the vapour phase.

I. PREFORMULATION[5]

The crucial first stage in creating pharmaceutical dosage forms that are stable, safe, and effective is preformulation research. They entail describing the drug's chemical and physical characteristics as well as those of any possible excipients. This facilitates the formulator's generation of helpful data that could otherwise impede the successful and fruitful development of an effective dosage form.

Objectives of Preformulation studies:

- To produce valuable data that will be required for the development of safe and stable dosage forms that can be produced commercially.
- To offer comprehensive information and comprehension of a proposed therapeutic molecule's physical properties before dosage form creation.

Goals of Preformulation studies:

- To determine a prospective therapeutic molecule's physical properties.

- To determine whether a potential medication compound is compatible with standard excipients.

IDENTIFICATION AND CHARACTERISATION METHODS[6,7]

Distribution of Particle Sizes: Particles in aerosols range in size from nanometers to micrometres. Particle behaviour in the atmosphere, health consequences, and light-scattering and light-absorbing capabilities are all influenced by their size distribution.

The tool Particles are categorised using an electrical mobility analyzer according to their size, charge, and electrical mobility. After being charged, particles are moved through a neutral laminar air flow and a high-voltage electric field. Smaller particles with higher mobility reach the detector later, while larger particles with lower mobility experience a smaller deflection in the airflow. The device measures the arrival time of particles to determine the size distribution of those particles.

Aerosol particles come in a variety of forms, including spherical, irregular, and fibrous, which affects their aerodynamic characteristics and how they interact with surfaces.

Density: The composition of aerosol particles influences their density, which in turn influences their settling velocity and behaviour in the atmosphere. Determining the aerosol's density during preformulation is crucial for comprehending its behaviour and maximising its dispersion. The density of the active pharmaceutical ingredient (API) can be measured empirically (using a pycnometer or gas displacement procedures) or through literature research. Solubility: An aerosol's solubility during preformulation is essential to its performance, stability, and ideal drug delivery. The solubility of API can be ascertained by equilibrium solubility techniques such as shake-flask or UV spectroscopy in a variety of pertinent solvents (water, alcohols, propellants, etc.).
Chemical Reactivity: Aerosols have the ability to react chemically with the atmosphere to generate new chemicals, haze, or secondary particles.

Toxicity: Assessing the toxicity of an aerosol during preformulation is crucial for ensuring the safety and regulatory compliance of the final product. The existing toxicological data for the active pharmaceutical ingredient, including in vivo and in vitro studies must be thoroughly reviewed.

EXCIPIENT DRUG COMPATIBILITY STUDY

Excipient-drug compatibility studies are an essential part of aerosol development's preformulation phase. The stability, effectiveness, and safety of the finished product may be impacted by interactions between the drug substance (API) and the excipients employed in the formulation, which are identified by these investigations. This study's primary objective is to identify the excipients that are incompatible with API. The following categories apply to drug-excipient interactions:

• Physical contact

• Interaction between chemicals

• Interaction between physicochemical Compatibility study methodologies:

• Fourier-transform infrared (FTIR) • Powder X-ray diffraction (PXRD)

• X-ray diffraction (XRD) • Differential scanning calorimetry (DSC)

CRITERIA FOR EXCIPIENT SELECTION

Pharmaceutical excipients are inert components used in pharmaceutical products that are essential to the preparation, production, and distribution of the active pharmaceutical ingredient (API). Although they don't directly affect pharmacology, they do add value to the finished product. The following are a few factors to take into account while choosing an excipient.

Drug compatibility: The excipient and active substance cannot interact chemically or physically to degrade or lose potency.

Solubilization: Certain excipients, such as cyclodextrins or co-solvents, can increase the drug's solubility in the propellant, hence increasing the drug's release and bioavailability.

Toxicity: For topical or inhaled use, the excipient must be safe and non-toxic, meeting all applicable safety regulations.

Regulatory compliance: The excipient needs to abide by all applicable laws and pharmacopoeial requirements for use in pharmaceutical aerosols

Cost-effectiveness: The excipient's performance and advantages should be weighed against its cost.

Availability: For dependable manufacture, the excipient needs to be easily accessible in a consistent amount and quality.

Handling ease: The excipient should be simple to work with and include into the formulation process for aerosols.

FORMULATION OPTIMIZATION TECHNIQUES

The optimum potential component and processing condition combinations are found via methodical processes known as formulation optimisation procedures, which yield pharmaceutical products with the desired qualities.

Design of a statistical experiment: Aerosol performance can be systematically investigated by using DoE approaches such as response surface methodology and factorial designs to examine the impact of different process and formulation parameters. This makes it possible to optimise processes effectively and identify the main variables influencing the finished output.

Testing in vitro: Particle deposition and medication release can be better understood by doing in vitro experiments with cascade impactors and cell cultures.

In vivo testing: To evaluate the safety and effectiveness of the optimised formulation, in vivo investigations in human subjects or animal models are necessary.

II. FORMUL ATION

A suspension of tiny liquid or solid particles in a gas, usually under pressure, is called an aerosol. A careful balancing act between substances and methods is required to create an aerosol that is both safe and effective.

An aerosol formulation's constituent parts are;

Propellant: The product is forced out of the container by this pressurised gas. Typical propellants consist of:

- Hydrofluoroalkanes (HFAs): Often found in pharmaceutical aerosols, these non-flammable, low-GWP molecules are good for the environment.
- Hydrocarbons: Historically well-liked for their excellent efficiency and cheap cost. But they also have disadvantages including high GWP, flammability, and other health risks. Environmental rules in certain areas are restricting their use more and more.
- Compressed air: Mostly utilised in medical and food aerosols when chemical propellants are not wanted. Although it doesn't burn and is safe for the environment, its pressure isn't very high, and it occasionally causes uneven spraying.

Solvents: In aerosol formulations, solvents have a crucial but frequently overlooked role. These adaptable ingredients ensure a homogenous and stable combination that may be administered from the container in an efficient manner by dissolving the other excipients and active ingredients. The following types of solvents are employed in aerosol formulation:

• Glycols (propylene glycol and glycerine);

• Alcohols (ethanol, isopropanol, and n-propanol).

Solvents with chlorine

Emollients: Using emollients in aerosol form is a quick and easy approach to prevent and moisturise dry, sensitive, or irritated skin. The main components, which are usually oils, fats, or waxes, act as a barrier to prevent moisture loss and relieve dry skin. Mineral oil, petrolatum, lanolin, and shea butter are typical examples.

Deodorants: The main goal of these compositions is to neutralise or disguise odour. They frequently include:

MANUFACTURING OF AEROSOL[8.9]

To create a variety of goods based on aerosols, particular procedures and techniques are used in the manufacturing of aerosols. The type of aerosol, its intended use, etc., determine which manufacturing processes are used. Several typical techniques in the production of aerosols are:

1. Cold filling process
2. Pressure filling process
3. Compressed gas filling process

COLD FILLING PROCESS:

The active components are either suspended or dissolved in a propellant and/or co-solvent to create the product concentrate. After that, this product is cooled to around -30°C. The previously cooled container is filled with the chilled product. The cylinder's propellant is forced to go through the chilling unit. The copper tubing in the chilling unit is coiled to enhance the surface exposed to cooling, and it is installed in an insulated box. Coils are put into a container that has been previously filled with acetone or dry ice, which acts as a cooling agent. Finally, the container is filled with the cold propellant. The container and valve assembly are crimped together.

Advantages:

This works with fluorocarbon propellants and can be used with both metered and non-metered valves.

• Compared to the pressure filling approach, this is easier.

• Compared to pressure filling, this technique is quicker.

Disadvantages:

- Some propellants may vaporize from the container before the crimping valve. Therefore it is not suitable for hydrocarbon propellants.
- An excessive amount of propellant escaping and vaporizing may form an explosive mixture at the floor level.

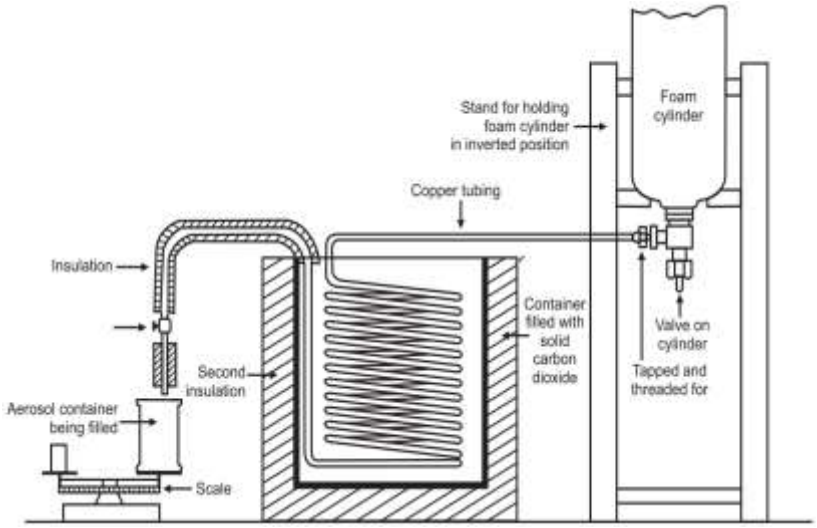

Fig 2: Cold fill apeparatus

PRESSURE FILLING PROCESS:

Prepare the product concentrate at room temperature. Measure the volume of the concentrate and add it to the can. Crimp the valve assembly to the can. Attach a propellant cylinder to the can's valve assembly. Pressurise the inlet valve at the bottom of the cylinder to add the desired amount of propellant. Allow trapped air to escape through the upper valve. The propellant will stop flowing when the burette and container's pressure equalise.

Advantages:

• There is a decrease in propellant escaping into space. It is therefore friendly to the environment.

• The process of filling is done at room temperature.

• Successful filling of solutions, emulsions, and suspensions is achievable, which is not achievable with cold filling techniques.

Disadvantages:

• Filling inhalation aerosols with a metered valve is not appropriate for this method; also, the process takes longer than cold filling.

• Rapid production rates are feasible.

Fig 3: Pressure fill apparatus

COMPRESSED GAS FILLING PROCESS:

Once ready, the product concentration is poured into the container. In its place, the valve is crimped. A hoover pump is used to remove the air from the container. After inserting the filling head into the valve aperture, the valve is depressed. The container is open to the gas's entry. The gas ceases to flow when the pressure inside the container reaches the delivery pressure.

A pressure-reducing valve is necessary because of the tremendous pressure that the compressed gases are under. A flexible hose with a filling head that can sustain pressure of approximately 150 pounds per square inch gauge (psig) is attached to the delivery gauge.

I. EVALUATION OF FORMULATION

FLAMMABILITY AND COMBUSTIBILITY

FLASH POINT:

In order to determine the flash point of an aerosol, two basic types are available which are an open cup and closed cup.

- Open cup tag apparatus: Flash point is done by reducing the temperature of the aerosol product to 25 F. The temperature at which vapour ignites in the test liquid is known as the "flash point," and it is allowed to gradually rise.
- Closed Cup Test: To find the temperature at which the sample flashes, the investigated sample is put into a sealed test cup and exposed to a possible ignition source.

FLAME EXTENSION:

Another name for it is the flame projection test. A fixed distance of 6 inches (15 cm) is used to spray the product into an open candle flame for approximately 4 seconds. The length of the flame projection is recorded and the flame's extension is measured in centimetres. If an aerosol product's flame flashes back to the actuator or extends 18 inches (46 cm) or more through an open flame, it is deemed flammable.

PHYSICO-CHEMICAL CHARACTERISTICS

VAPOUR PRESSURE:

Differential scanning calorimetry is one method that can be used to find an aerosol's vapour pressure (DSC). By measuring the difference in the amount of heat needed to raise the temperature of a sample and a reference as a function of temperature, differential scanning calorimetry is a thermoanalytical technique.Throughout the experiment, the temperature of the sample and reference are kept almost constant.

DENSITY:

Both a hydrometer and a pycnometer can be used to measure the density of aerosol. Based on the idea of buoyancy, an instrument called a hydrometer or lactometer is used to measure the density or relative density of liquids. Usually, they are graduated and calibrated using one or more scales, like specific gravity.

MOISTURE CONTENT:

The Karl Fischer method can be used to determine the aerosol's moisture content. Iodine and sulphur dioxide undergo an oxidation process, which is the basis of the Karl Fischer titration method. The Karl Fischer method measures moisture content by reacting quantitatively and selectively with water using the Karl Fischer reagent. Iodine, sulphur dioxide, a base, and a solvent—such as alcohol—make up the Karl Fischer reagent.

II.STABILITY STUDIES

The ability of a certain formulation in a certain container/closure system to maintain its physical, chemical, microbiological, etc. properties is known as pharmaceutical product stability. Incorporating quality, efficacy, and safety into a medicine formulation requires a sophisticated set of processes that are expensive, time-consuming, and need scientific knowledge.

STABILITY TESTING METHODS

Real-Time stability testing:

For real-time stability testing, a longer test period is typically used to allow for significant product degradation under advised storage settings. The length of the test depends on the product's stability, which needs to be sufficient to show unequivocally that no detectable deterioration takes place and to allow one to discern degradation from inter-assay variance. Data is gathered during testing at a suitable frequency to enable trend analysis to differentiate between daily ambiguity and instability. By using a single batch of reference material whose stability properties have already been determined, the reliability of data interpretation can be strengthened. The consistency of the performance and the stability of the reagents are also aspects of the reference material's stability.

Accelerated stability testing:

Accelerated stability testing involves stressing a product at multiple high (higher than ambient) temperatures in order to calculate the minimum amount of heat input necessary for the product to fail.

This is done in order to put the product in an environment that speeds up deterioration. Next, shelf life is estimated using this data, or it can be used to contrast the relative stability of different formulations. This typically shortens the development schedule by giving an early indication of the product shelf life. During accelerated stability testing, stress factors such as moisture, light, agitation, gravity, pH, and packing are applied in addition to temperature.

Cyclic temperature stress testing:

For marketed items, this is not a standard testing procedure. Using this approach, cyclic temperature stress tests are created based on product knowledge to replicate possible market storage circumstances. Since the diurnal rhythm of the earth is 24 hours, which the marketed medications are most likely to experience during storage, the time of cycle that is primarily examined is 24 hours. It is advised that the lowest and maximum temperatures for the cyclic stress testing be chosen product by product, taking into account things like the product's suggested storage temperature and unique physical and chemical degradation characteristics. Additionally, it is advised that the test typically consist of 20 cycles.

CONCLUSION

On aerosols, a thorough investigation was done. prescription drugs Products known as aerosols are pressure-packed mixtures of medicinally active substances that release when the proper valve system is activated. We outline the GLP and GMP standards for aerosol in this study. Preformulation investigations were also examined, including drug identification and characterisation procedures, drug compatibility tests including excipients, selection criteria for excipients, formulation and optimisation methods, and formulation. Studies on packaging and labelling specifications, stability studies, SOPs, and evaluation studies were also conducted.

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