IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Spray Dried Microparticles As Carriers For Pulmonary Drug Delivery

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ABSTRACT:

Pulmonary drug delivery is an effective non-invasive approach for treating local and systemic diseases by delivering drugs directly to the lungs. The lungs' large surface area, rich vascularization, thin alveolar membrane, and avoidance of first-pass metabolism enable rapid absorption, enhanced bioavailability, reduced systemic side effects, and improved patient compliance. Dry powder inhalers (DPIs) are widely used because of their stability and convenience. Various techniques, including spray drying, spray freeze drying, freeze drying, solvent evaporation, supercritical fluid technology, and emulsification, are used to prepare inhalable microparticles, with spray drying being the most preferred due to its ability to produce particles with suitable aerodynamic properties for deep lung deposition. These microparticles are characterized by FTIR, DSC, SEM, particle size analysis, zeta potential, micromeritic properties, drug loading, entrapment efficiency, in vitro drug release, and aerosol performance. Natural, synthetic, and biodegradable polymers are used to improve particle stability, drug encapsulation, controlled release, and lung deposition. Inhalable microparticles have been widely investigated for the pulmonary delivery of bronchodilators, corticosteroids, antibiotics, antifungals, vaccines, proteins, peptides, anticancer drugs, and gene therapeutics. This review highlights pulmonary drug delivery, lung deposition mechanisms, inhalation devices, preparation methods, characterization techniques, and recent advances in spray-dried inhalable microparticles for targeted and efficient respiratory drug delivery.

Key Words: Microparticles, systemic drug delivery, controlled drug release, drug encapsulation, dry powder inhalers

INTRODUCTION:

PULMONARY DRUG DELIVERY SYSTEM :

Pulmonary drug delivery is a promising and evolving technology in which drugs are inhaled through the lungs and absorbed into the systemic circulation via the alveolar epithelium. It is an attractive, non-invasive route commonly used to treat respiratory diseases by delivering drugs directly to their site of action, thereby reducing the required therapeutic dose. Besides local therapy, the pulmonary route can also be used for systemic drug delivery, such as inhaled insulin. Successful pulmonary delivery depends on factors including particle size, bioavailability, device compatibility, and formulation stability, along with the use of an appropriate inhaler device capable of generating aerosols with particle or droplet sizes suitable for deposition in the targeted region of the lungs.1,2

Advantages of Pulmonary Drug Delivery : 3,4

1. Direct Drug Delivery to the Target Site: Delivers drugs directly at the disease site, in

diseases like asthma and COPD, reducing systemic side effects.

2. Rapid Onset of Action : The lungs' large surface area and rich blood supply enable quick

drug absorption, making this route ideal for fast-acting therapies.

3. Avoidance of First-pass Metabolism: Drugs delivered through the lungs bypass the liver's

first-pass metabolism, improving bioavailability and effectiveness of certain drugs.

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APPROACHES IN PULMONARY DRUG DELIVERY :

Particulate carriers such as liposomes, microparticles, and nanoparticles improve the therapeutic index of drugs by modifying absorption, reducing metabolism and toxicity, and prolonging biological half-life. In these systems, drug distribution depends mainly on the carrier properties rather than the drug itself. Effective pulmonary delivery requires appropriate carrier selection, production methods, delivery devices, and consideration of lung physiology and clinical needs.

5-7 . Pulmonary drug delivery offers a non-invasive, patient-friendly alternative that improves therapeutic efficiency and patient compliance.

❖ MICROPARTICLES :

The microparticulate delivery system are considered and accepted as a reliable means to deliver the drug to the target site with specificity and to maintain the desired concentration at the site of interest without untoward effects. Micro-particles are the polymeric entities falling in the range of 1-1000µm. 8

- **Properties of Ideal Microspheres:** 9

a. The ability to incorporate reasonably high concentrations of the drug.
b. Stability of the preparation after synthesis with a clinically acceptable shelf life.
c. Controlled particle size and dispersibility in aqueous vehicles for injection.
d. Release of active reagent with a good control over a wide time scale.
e. Biocompatibility with a controllable biodegradability and
f. Susceptibility to chemical modification.

- **Advantages of Microparticles :** 10

1. Protection of unstable, sensitive materials from their environments prior to use.
2. Better processibility (improving solubility, dispersibility, flowability).
3. Self-life enhancement by preventing degradative reactions.
4. Masking of odour or taste.
5. They increased the relative bioavailability of drugs.
6. The formulation of microparticles also provides the method of targeting the drug delivery to specific sites.
7. The microparticles hold great potential in reducing the dosage frequency & toxicity of various drugs.
8. They provide the sustained release formulation with lower dose of drug to maintain plasma concentration & improved patient compliance.
9. They also have an advantage of being stored in dry particle or suspension form with little or no loss of activity over an extended storage period.
10. Limiting fluctuation within therapeutic range.

CATEGORIES OF MICROSPHERES :

- **Mucoadhesive Microspheres :**

These are of 1-1000mm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it, respectively. Microspheres, in general, have the potential to be used for targeted and controlled release drug delivery; but coupling of mucoadhesive properties to microspheres has additional advantages, e.g. efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies, etc. on the surface of the microspheres. 11

As these dosage forms facilitate intimate contact of the formulation with underlying absorption surface thus allows modification of tissue permeability for absorption of macromolecules, such as peptides and proteins. Inclusion of penetration enhancers such as sodium glycocholate, sodium taurocholate and L-lysophosphotidyl choline (LPC) and protease inhibitors in the mucoadhesive dosage forms resulted in the better absorption of peptides and proteins.12

Mucoadhesive dosage forms also prolong residence time of the dosage form at the site of application and absorption to permit once or twice a day dosing. 12

- **Floating Microspheres :**

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies. 11

- **Radioactive Microspheres:**

They are injected to the arteries that lead to tumor of interest. So all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues.12

- **Bioadhesive Microspheres :**

Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc. can be termed as bioadhesion. Adhesion of bioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration. 11,12

- **Magnetic Microspheres :**

This type of delivery system is very important which localises the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. Magnetic microspheres can be filled with drugs or radioactive materials to treat a variety of illnesses. Magnets applied outside the body attract the spheres to the disease site where they deliver therapeutics in a targeted way. The magnets attract the microspheres to the immediate area of the wound site and stop them there. The spheres gradually break down and release growth factors over a period of weeks, allowing blood vessels and damaged tissues to regrow and repair.13

METHODS OF PREPARATION OF MICROPARTICLES : 14

Following are the various methods for preparing microparticles :

1. Single Emulsification Technique.
2. Double Emulsification Technique.
3. Normal Polymerization Technique.
4. Interfacial Polymerization Technique.
5. Phase Separation Coacervation Technique.
6. Spray Drying and Spray Congealing Technique.
7. Solvent Extraction Method.
8. Solvent Evaporation.
9. Wet Inversion Technique.
10. Complex Coacervation.
11. Hot Melt Microencapsulation.
12. Ionotropic gelation technique.

PULMONARY DRUG DELIVERY DEVICES :

The lung has served as a route of drug administration for thousands of years. The origin of inhaled therapies can be traced back 4000 years ago to India, where people smoked the leaves of the Atropa belladonna plant to suppress cough. In the 19th and early 20th centuries, asthmatics smoked asthma cigarettes that contained strontium powder mixed with tobacco to treat the symptoms of their disease. The development of modern inhalation devices can be divided into three different categories, the refinement of the nebulizer and the evolution of two types of compact portable devices, the metered-dose inhaler (MDI) and the dry powder inhaler (DPI). 15

The advantages and disadvantages of each system will be discussed below :

❖ **NEBULIZER:**

Nebulizers are commonly used for the treatment of asthma and other respiratory diseases. They convert liquid medication into fine droplets that can be inhaled directly into the lungs. The two main types of nebulizers are jet nebulizers and ultrasonic nebulizers.

Jet nebulizers work on the Bernoulli principle, where compressed air or oxygen passes through a narrow opening and creates low pressure that pulls the drug solution from the reservoir and breaks it into small droplets. Ultrasonic nebulizers use a piezoelectric crystal vibrating at a high frequency (1–3 MHz) to produce aerosol droplets; higher frequencies generate smaller droplets. Jet nebulizers can deliver most drug solutions and large doses with minimal patient coordination.

However, only about 10% of the drug reaches the lungs, while the remaining drug is either left inside the nebulizer as dead volume or lost during exhalation. 16

❖ **INHALERS :**

The medicine inside an inhaler goes straight into the airways. Therefore it needs much smaller dose than took the medicine as a tablet or liquid by mouth. Inhalation represents an attractive, rapid and patient-friendly route for the delivery of systemically acting drugs, as well as for drugs that are designed to act locally on the lungs themselves.

➢ **Dry Powder Inhalers (DPI) :**

Interest in DPIs as an effective, efficient and environmentally friendly way of delivering drugs to the lung has accelerated in recent years. A fundamental difficulty with developing solid state aerosols, or DPIs, is managing both the ubiquitous and the transient forces contained in powder beds. Indeed, managing such particulate forces, for example via particle engineering techniques, is now considered central to successful DPI formulation and production. In consequence, much attention is currently focused on producing “smart” formulations, where it may be possible to achieve excellent powder flow and low cohesive forces. However, having an efficient and robust formulation technology in the laboratory is only a start on the road to producing a successful DPI product. 17

Pharmaceutical scientists all too frequently meet major obstacles when they engage in the world of DPI product design – not least because of the further complications of this area resulting from the plethora of DPI device designs. There is tremendous variation in the methods used to store and meter powders and to generate the aerosol cloud. In the case of DPI aerosol generation, there is a great deal of variation between different types of device, in the fluid dynamic and electrostatic environment that the powder formulation experiences. 18

- **Applications of DPIs :** 19

A dry powder inhaler (DPI) is a device used to deliver medication directly to the lungs in the

form of a dry powder. Here are some of its primary uses:

1. Treatment of Asthma: DPIs are commonly used to deliver bronchodilators (e.g., salmeterol)

and corticosteroids (e.g., budesonide) to help open airways and reduce inflammation.

2. Chronic Obstructive Pulmonary Disease (COPD): DPIs provide medications that relax muscles in the lungs and reduce mucus production for those with COPD.

3. Pulmonary Fibrosis: DPIs are used to deliver antifibrotic drugs to help slow the progression of the disease.

PARTICLE ENGINEERING TECHNIQUES FOR INHALABLE MICROPARTICLES :

It is challenging to prepare dry powder for inhalation, especially within the most desired particle size range of 1–5 μm. 20,21

Researchers have studied many techniques to achieve this. Among all these mentioned techniques milling and spray drying are mostly used in pharmaceutical companies to prepare dry powder for inhalation (DPIs). 22-27

1. Spray drying technique
2. Spray freeze drying method
3. Supercritical fluid technology
4. Milling
5. Solvent precipitation method
6. Double emulsion / solvent evaporation technique

❖ SPRAY DRYING

Spray drying is the process in which the emulsion, solution or any other pharmaceutical preparation get converted into powder form as in nanoparticle or microparticles and these nanoparticles or microparticle are further use to prepare tablet, capsule or in powder form. Spray drying is a notable technique for particle production which comprises on the change o a liquid material into dried particles. 28

Concept of spray drying technique depending upon the removal of solvent or the cooling of solution the two processes are spray drying & spray is congealing. Spray drying is the most widely used industrial process involving particle formation and drying.

- **Principle** : 29

Three steps involved in spray drying:

1. Atomization: of a liquid feed change into fine droplets.
2. Mixing: it involves the passing of hot gas stream through spray droplets which result in

evaporation of liquids and leaving behind dried particles.

3. Drying: Dried powder is separated from the gas stream and collected.

- **Working :**

These processes are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent this processes are named spray drying. In spray drying, the polymer is dissolved in a volatile organic solvent such as dichloromethane, acetone etc. The drug in solid form is dispersed in the polymer solution with high speed homogenization. This dispersion is then subjected to atomization in a stream of hot air. The atomization leads to the formation of small droplets or the fine mist from which the solvent evaporates instantaneously leading to the formation of the microspheres in a size range 1-100µm.

- **Advantages :**

1. Rapid drying process.
2. Materials can be directly dried into powder.
3. It is easy to change the drying conditions and adjust product quality standards.
4. There is a certain negative pressure in the drying room, which guarantees the hygienic conditions in the production, avoids the dust flying in the workshop, and improves the purity of the product.
5. High production efficiency and fewer operators.
6. Large production capacity and high product quality. The spray volume can reach several hundred tons per hour.

- **Limitation :-**

1. The equipment is complex, covers a large area, and requires a large investment.

2. The price of a spray dryer and powder recovery device is relatively high.

3. The thermal efficiency is not high and the heat consumption is large.

- **Application :** 30

Spray drying is widely used in the pharmaceutical and food industries because spray drying machines meet GMP requirements of these two fields and has excellent performance.

CHARACTERIZATION OF MICROPARTICLES : 31,32

- ## Percentage Yield :

Evaluated by taking spray dried microcapsules accurately weighed, and considering the total amount of drug and polymers used for preparing the feed solution, the yield of production was calculated, as a percentage.

- ## Flow Properties :

Flow properties of powders are important for uniform dosing, filling, and aerosolization (especially in dry powder inhalers). These properties are assessed using bulk density, tapped density, Carr's index, Hausner ratio, angle of repose. 33

1. **Bulk Density :**

Bulk density is an important property of powders, granules, and other particulate materials used in pharmaceutical and industrial applications. It is defined as the mass of a powder divided by the total bulk volume occupied by the powder, including the volume of the particles, interparticle void spaces, and internal

pores. Bulk density is not an intrinsic property of a material because it varies depending on particle arrangement, handling, packing, and compaction. The determination of bulk density is significant in evaluating powder flow properties, packaging, storage, processing, and equipment design in pharmaceutical manufacturing. Bulk density is commonly expressed in grams per milliliter (1 g/mL = 1 g/cm3 = 1000 kg/m3

Bulk density = mass/volume

2. **Angle of Repose :**Angle of repose was determined by fixed funnel method. In this method, specific amount of microcapsules was passed from funnel onto a paper. The height (h) and radius of the cone formed on graph paper were measured and angle of repose was calculated by following equation. Tan θ = h/r

3. **Hausner's Ratio :** The Hausner ratio can be defined as the ratio of the tapped bulk density to the apparent (aerated/poured) bulk density. Higher values of the ratio indicate poor flowability of the powder.

Hausner ratio = tapped bulk density / poured bulk density

- **Particle Size and Shape:**

The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). The prepared microcapsules were examined by optical microscopy using eye-piece micrometre. The eyepiece is calibrated with the help of stage micrometre. The mean diameter and particle size distribution of each formulation were measured by determination of the martin's diameter of 100 randomly selected particles. 32,33

- **Electron Spectroscopy for Chemical Analysis:** The surface chemistry of the microspheres can be determined using electron spectroscopy for chemical analysis (ESCA).
- **Density Determination:** The density of the microspheres can be measured by using a multi-volume pycnometer.
- **Isoelectric Point:** The micro electrophoresis is used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined.
- **In vitro methods:** Release studies for different types of microspheres are carried out by using different suitable dissolution media, mostly by rotating paddle apparatus (USP /BP).
- **Drug Loading (%) :** 108 Drug loading is calculated by total amount of drug used to the total recoverable final weight of microspheres.
- **Drug entrapment efficiency:** Drug entrapment efficiency can be calculated using the following equation, % Entrapment = Actual content/Theoretical content x 100.
- **Swelling index:** The swelling index of the microsphere was calculated by using the formula, Swelling index = (mass of swollen microspheres – a mass of dry microspheres/mass of dried microspheres) 100.

FUTURE SCOPE :

The future scope of spray-dried microparticles in pulmonary drug delivery is highly promising due to their potential to improve therapeutic efficacy, provide sustained drug release, and enhance patient compliance in asthma and COPD treatment. Further research can explore biodegradable and biocompatible polymers, novel excipients, and surface modification techniques to improve stability, deep lung deposition, and reduce particle clearance. In vivo, pharmacokinetic, bioavailability, and clinical studies are needed to evaluate pulmonary deposition, safety, efficacy, and dose optimization. Combination therapy with bronchodilators or anti-inflammatory drugs may further enhance therapeutic outcomes. Advanced formulation technologies and analytical approaches can improve reproducibility, quality control, and overall formulation performance, supporting the development of effective targeted pulmonary drug delivery systems with reduced systemic side effects. With continued research on large-scale production, safety evaluation, and regulatory approval, nanosponges are expected to play a significant role in next-generation drug delivery systems

CONCLUSION :

Spray-dried microparticles have emerged as a versatile and efficient platform for pulmonary drug delivery, offering precise control over particle size, morphology, density, and aerodynamic properties for effective lung deposition. Spray-drying enables the production of stable, highly dispersible dry powders with reproducible manufacturing characteristics suitable for dry powder inhalers. These systems provide sustained and targeted drug delivery, improved bioavailability, reduced systemic side effects, and enhanced patient compliance in the treatment of diseases such as asthma, COPD, cystic fibrosis, pulmonary infections, and lung cancer. Moreover, their ability to encapsulate diverse therapeutic agents, including small molecules, biologics, vaccines, and nanocarriers, expands their clinical potential. Despite challenges related to stability, scale-up, device compatibility, and regulatory requirements, continued advances in particle engineering, formulation strategies, and manufacturing technologies are expected to further strengthen the role of spray-dried microparticles in next-generation pulmonary drug delivery.

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