A TECHNOLOGICAL REVIEW ON DRY POWDER INHALER FORMULATIONS WITH AND WITHOUT CARRIERS

By

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
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Ethics Statement

No trial animal was harmed during this study.

Abstract/ Executive Summary

This review mainly focuses on the advanced technologies used in the development of dry powder inhaler (DPI) formulations. There are several conventional techniques existing till date which were used to develop DPI formulations. But they have become ineffective to deal with current problems. Therefore, in this review modern technologies of DPI formulations with or without carriers have been discussed briefly to figure out the better one based on their advantages and disadvantages such as pulmosphere is a technique which gives the drug particles a smooth surface texture and the deposition is considered enough to be effective in the body on the other hand spray drying gives good amount of deposition in the lungs by providing carriers with coarse surface and by increasing the flow ability. Though no technology is perfect but most of these advanced technologies are giving better results in case of deposition in the lungs than the past methods. Also, these technologies are on their way for further development in future in terms of better flow ability, less aggregation, higher deposition and lower toxicity in the body. To conduct this study, Science Direct, Sci-Hub have been used for collecting the scientific evidence and experimental data regarding the review.

Keywords: Drug Formulation; Particle Engineering; Flow Property; Fine Particle Fraction; Pulmonary Delivery.

Dedication

Dedicated to my parents and brothers

Acknowledgement

I would like to begin by thanking the Almighty Allah, our creator, the source of our life, strength, knowledge, wisdom, blessings and mercy. All praises to the Almighty Allah for blessing me with immense patience and strength to complete this project. This project would not have been completed without the support of the people who are recognized here.

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Table of Contents

List of Tables

List of Figures

List of Acronyms

ASES	Aerosol Spray Extraction System
AD	Aerodynamic Diameter
BUD	Budesonide
CI	Carr's Index
COPD	Chronic Obstructive Pulmonary Disease
CFC	Chlorofluorocarbon
DPI	Dry Powder Inhaler
DSPC	Distearoylphosphatidylcholine
FPF	Fine Particle Fraction
FP	Flow Property
HGCAP	High-gravity Controlled Antisolvent Precipitation
MMAD	Mass Median Aerodynamic Diameter
PLGA	Poly Lactic-co-glycolic acid
RESS	Rapid Expansion of Supercritical Solution
SAS	Supercritical Anti-solvent
SF	Supercritical Fluid
SPG	Shirasu Porous Glass
SEDS	Solution Enhanced Dispersion by Supercritical Fluid

Chapter 1

Introduction

1.1 Background

There are many ways to deliver drugs in our body such as orally, topically, intravenously and by inhalation. For delivering drugs directly into our lungs by inhalation a medical device is used called inhaler. There are many types of inhalers used by patients and there is a long history behind its advancement and development throughout the years which will be discussed in the following section.

Therapeutic drug administration by inhalation covers a long history (Grossman 1994). About 4000 years ago in India, people used durata stamonium and durata ferox in a powdered form along with ingredients like ginger and pepper for the purpose of smoking. In 1764 Philip Stern recognized that, only method to deliver medicine to the lungs was by the windpipe (Sanders 2007) and because of that, respiratory treatment gained a lot of attention (Sanders 2007). Afterwards, ceramic inhaler was first made in the 18th century. Then in early 1900, for bronchodilation, hand bulb nebulizer was used to deliver adrenaline chloride in the lungs. Later in the 20th century ultrasonic and electronic nebulizers were developed (Geller, Weers, and Heuerding 2011).

The concept of metered dose inhaler (MDI) came in 1956, which was driven by propellants (Dessanges 2002). It became extensively popular as it was small, inexpensive, fast, silent and easy to use (theoretically). However, patients were facing difficulty while using this inhaler as they were unable to operate it correctly. The major concern began in the early 1970s when it was proven that chlorofluorocarbon (CFC) propellant used in the MDI was responsible for

ozone layer depletion in the stratosphere (Ultraviolet 1974). This resulted in Montreal Protocol, which came into force in 1989 and ordered to phase out all the substances depleting the ozone layer. Because of this incident, dry powder inhaler (DPI) became popular among the mass as it didn't need to use any propellant like MDIs.

1.2 History of DPI

Dry Powder Inhalers are acknowledged from Vincent Alfred Newton's UK patent 1161 since mid-18th century. His DPI device was intended to deliver pulverized potassium chloride, which didn't happen in reality. After 100 years in 1948, Abott discovered aero haler, to deliver penicillin and norethisterone to the lungs (Sanders 2007). Inhalers in between 1950 to 1980 resembled same design and type as aero haler. These thirty years DPI formulation was lactose based with smaller drug particles (approximately 1-5 micron) placed in capsules. In 1967, Fisons Spinhaler® was the first device to be marketed in the 1950 to 1980s period. The specialty of this device was that it could accommodate 20 mg dose of cromoglycate sodium which was higher than MDIs (Robson and Taylor 1981). Many patents for the design of highly efficient inhalers were filed in this period. But all the patents that were accepted had a similar basic design of the device and even the formulation was same (Clark 2007). Like other inhalers, new patent designs in that period had same gelatin capsule and lactose as carrier for the drug formulation. Clearly there were some differences such as the way of piercing of the capsule or the way capsule was spinning and vibrating while releasing the content during inhalation. Later, in 1969 Rotahaler® (Izbicki et al. 1999), in 1980 Inhaler Ingelheim by Boehringer Ingelheim and in 1990 Cyclohaler® was launched. Furthermore, diseases like Asthma and Chronic Obstructive Pulmonary Disease (COPD) needed microgram drug dose to be delivered to the lungs which was impossible without carriers. Hence, it was defined by Jones and Pilpel (Sadoc et al. 2010) that the mixing of microgram drug with bigger carriers are required which will cause adhesion of drug on the surface of the

carrier (de Boer et al. 2017). This mixing was studied by shotton and Orr and also by Travers and White in 1971 (Polytechnic, Building, and Terrace 1978). Then, in 1975 Hersey recognized that this kind of mixing for the preparation of the formulation for DPIs are not same as the so called "Random mixing" so he named this mixing "Ordered mixing"("Victorian College of Pharmacy, 381 Royal Parade, Parkville, Victoria 3052 (Australia) (Received May 16, 1974)" 1974). Later on "Ordered" was replaced by "Adhesive" (Staniforth 1987). In 1990s multi dose reservoir inhalers were introduced with different dose measuring principles like cylinders such as Easyhaler® from Orion Pharma (Meakin et al. 2009), disks such as Pulvinal® from Chiesi Farmaceutici (Meakin et al. 2009) etc. Adhesive mixture was also applied to the first Multi dose unit inhaler in 1990.The only exception to this system was Turbuhaler® from Astra. Later on carrier free formulation was introduced for the delivery of drugs to the lungs. Almost all the Inhalers used till 2010 was passive or breathe actuated devices.

In the last 10-15 years the concept of inhalers had undergone an enormous development. Currently many developments can be seen in Dry Powder Inhalers (de Boer et al. 2017) such as:

1. Availability of powder filling equipment.
2. New developed technologies for both with and without carrier formulations.
3. High dose formulations.
4. Emerging expertise for more efficient device.
5. Understanding pulmonary drug deposition and distribution.

1.2.1 Dry Powder Inhalers (DPIs)

Inhalers that deliver medication in a dry powder form are called DPI. DPIs are breath-actuated devices, which depend on your inhalation, to release the medication from the device.

In comparison to the pMDIs, these are easier to use as they don't need propellants and co-ordination. Usually, DPIs are single dose devices, although multi-dose DPIs are available as well.

1.2.2 Respiratory tracts

The process of gas exchange in our body, functions through the lungs and the respiratory system. Respiratory tracts consist of larynx, trachea, bronchi and alveoli.

Aerosol drug particles after actuation, first passes our mouth then our throat which is a part of our pharynx. After that, particles from throat goes to our trachea, which divides as bronchus into our lungs. Bronchus further divides into bronchi and bronchioles. Bronchus, bronchi and bronchioles are air ways situated in our lungs through which particles finally enters into the alveolar from where drug absorption to the systemic circulation takes place (Self-assessment and Particles 2016).

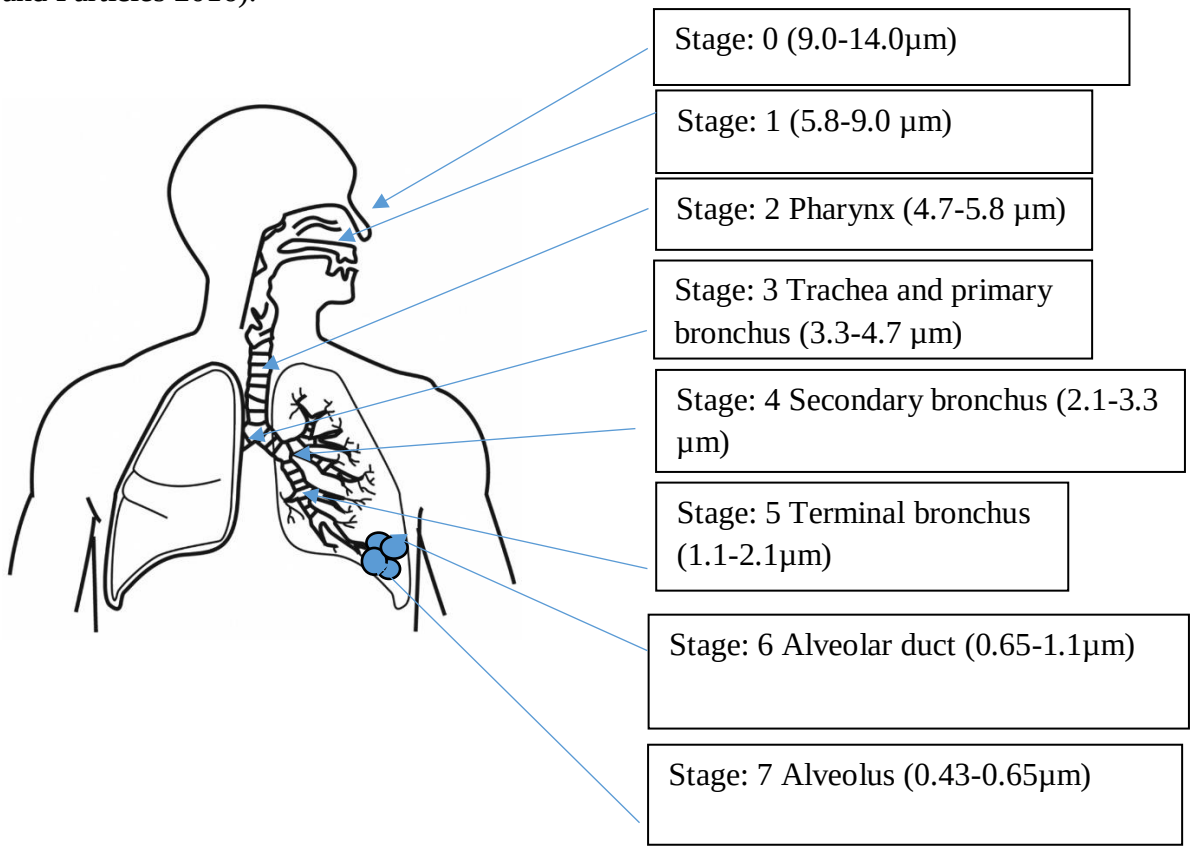

Figure 1: Respiratory system (Self-assessment and Particles 2016).

1.2.3 Drug delivery and deposition in the lungs

When inhaler is actuated, particles pass through respectively mouth, pharynx and trachea to the lungs. After reaching the lungs, drug particles absorbed from the alveolar region to the systemic circulation. But before particles goes to the alveolar region, they deposit into bronchus, bronchi and bronchioles (smaller airways). Smaller particles (within 1-5 micrometer or less than that) deposits into the smaller airways leading to higher absorption and larger particles deposits into the larger airways leading to lesser absorption (Newman and Chan 2008).

Hence, drug delivery and deposition to the lungs are complex procedures. Reasons are respiratory tracts defense mechanism (mechanical, chemical and immunological barriers) and behavioral barrier (Newman 2017).

Mechanical, chemical and immunological barriers are the barriers which inhaled drug particles face because of lungs defense mechanism.

Mechanical barrier

For drug to deliver in the lungs, mouth is the ideal place for inhaled drug particles. Lungs formation is complex, it consists of branching airways called bronchial trees. Particle has to enter to the alveolated region then to the large epithelial target site. After that, particle has to go through many airway bifurcations where deposition can takes place. For a particle to enter into the lungs, the size range is 1-5 micrometer and for delivery to the alveolar epithelium the size have to be less than 3 micrometer (Newman 2017). Though the deposition is influenced by some parameters such as inhaled flow rate, inhaled volume etc. Flow rate is a very much of a crucial parameter. For pMDIs flow rate have to be slow on the contrary, for DPIs flow rate have to be very fast (Lee et al. 2015). Mechanical barriers are a big issue in case of diseases that causes airways narrow down such as bronchoconstriction, mucus hypersecretion

etc. Muciliary clearance is a natural lung defense mechanism to get rid of deposited particles from the lungs to the oropharynx (Ganesan, Comstock, and Sajjan 2013). It can be a problem for the delivered and deposited drugs but this mechanism can be helpful if it moves the deposited drugs to the less favorable targeted sites.

Chemical and immunological barriers

Drugs should be deposited into the lungs for further action but deposited drugs can be exposed to the chemical actions for example photolytic enzymes (Labiris and Dolovich 2003). These enzymes may inactivate proteins and peptides in the lungs (Labiris and Dolovich 2003). Undissolved drug particles can be exposed to alveolar macrophages. Macrophages can engulf drug particles and remove them from lungs by lymph system. Surfactants present in the lungs can prevent particle adhesion to the lung surface and make them more available for the macrophages (Newman 2017).

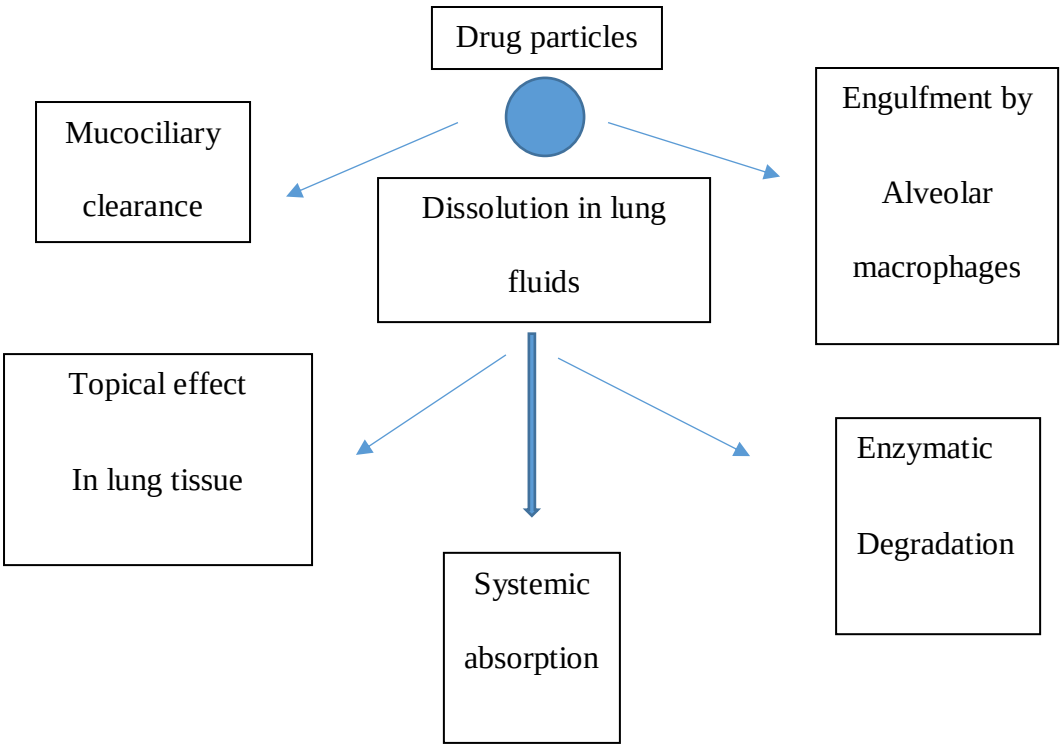

Figure 1: Schematic diagram showing barriers for deposited drug particles (Newman 2017).

Behavioral barriers

Behavioral barriers main reasons are patient's non adherence to the regimen and poor inhaler technique (Newman 2017).

Even if all the factors are right and drug can surpass all the barriers in the lungs, if a patient can't use inhaler properly then all the drugs will be deposited in the oropharynx not in the lungs also to get proper treatment, the patient must be adhered to their regimen (Newman 2017).

1.2.4 Twin stage impinger

Twin stage impinger (TSI) is a mimic of human respiratory tract. TSI is a device separated into two stages to assess the delivery of drugs into the lungs by MDIs or DPIs. It is an in vitro test. Discharged aerosol is fired through a simulated oropharynx, then by an impinger stage of defined aerodynamic particle size cut-off characteristics such as: andersen cascade impactor. Lower impinger collects the penetrated fine fractions which are within the range of 1-5 micrometer and also lesser than that.

The first impinger was a multistage liquid impinger (MLI). It developed to become twin stage impinger. TSI has two stages separated glass. Stage one implicates throat and stages 1 and 2 of MLI and stages two implicates stage 3 and 4 of MLI with a filter. Filter is required to elude problems related to drug recovery and after inhalation possible blockage in the filer. Two types of TSI are available. Type 1 have 60 L min-1 air flow and has been used for product development and quality control. To make type 1 simple by eradicating some stages type 2 was developed. In type 2 impinger quick fit inlet action can be observed in the new throat with better reproducibility and good air seal is provided by moulded rubber adaptor for the inhaler mouthpiece which gives an improved location and centring of the inhaler. For separated throat assessment, it can be separated by upper impinger. Type 2 also allows

smaller quantity of formulation to be used for avoiding loss and simplifying the drug removal (G. W. Hallworth, and D. G. Westmoreland 1988).

We can calculate the emitted drug dose, recovered dose from lower impinger and also the FPF of the formulation in a TSI.

Aerodynamic Diameter:

The aerodynamic diameter of a particle is designated as the diameter of a spherical particle having a density of 1000 kg/m3 which has same settling velocity as the particle of interest. This is a crucial particle characteristic for defining respiratory deposition (G. W. Hallworth, and D. G. Westmoreland 1988). Equation to calculate aerodynamic diameter:

$$dpa = dps\ (\rho p)^{\frac{1}{2}}$$

dpa = Aerodynamic particle diameter (µm)

dps = Stokes diameter (µm)

ρp = Particle density (g/cm3)

Fine particle fraction:

Fine particle fraction is the fraction of emitted particles (within the range of 1-5 micrometer) achieving deposition in the lower respiratory tracts (Finlay, Stapleton, and Zuberbuhler 1997).

Calculation of the emitted dose (ED), Recovered dose (RD) and FPF for TSI is given below:

$ED = \{(S1+S2) \div RD\} \times 100$ $FPF = (S2 \div RD) \times 100$

S1= Stage one S2= Stage two

Different impingers have different flow rates such as: anderson impinger has a flow rate of 28.3 L/min, multi-Stage Liquid Impinger has a flow rate of 15-100 L/min and next

Generation Pharmaceutical Impactor has a flow rate of 60 L/min (G. W. Hallworth, and D. G. Westmoreland 1988).

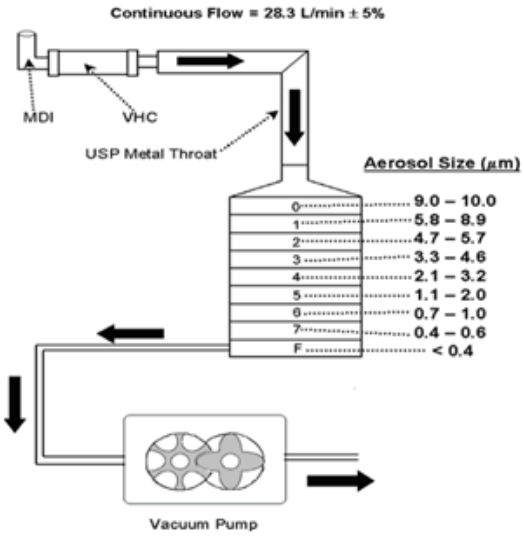

Figure 2: Andersen cascade impactor (G. W. Hallworth, and D. G. Westmoreland 1988).

Formulations with agglomeration or serious crystal growth can be detected easily by TSI. It is also used in quality assessment of aerosols during product development, for testing stability and for quality assurance and comparison of commercial products (G. W. Hallworth, and D. G. Westmoreland 1988).

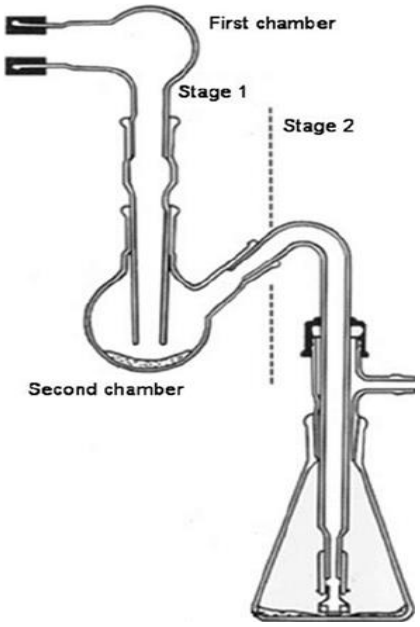

Figure 3: Twin stage impinger (G. W. Hallworth, and D. G. Westmoreland 1988).

1.2.5 Different types of DPIs with their device description

Revolizer

Among DPIs revolizer is the most easy to use. Medication capsules known as Rota caps are used with revolizer. It offers an accurate medication dose and a more efficient dispersal, even when the inhalation flow rates are low (Kondo et al. 2017).

Rotahaler

Rotahaler is a completely transparent DPI. Medication capsules known as Rota caps are used with rotahaler. It's really simple to use and as it is transparent so it enables us to make sure that we have inhaled the full medication (Kondo et al. 2017).

Multihaler

We don't need to insert a capsule each time we take a dose from multihaler as it is comprised of preloaded doses in a blister strip (Kondo et al. 2017).

When the device is twisted, blister is pierced and dose is released. It consists of a dose counter that helps to display the number of doses remaining in the device (Kondo et al. 2017).

Breath Actuated Inhalers (BAIs)

pMDI technologies advanced form is Breath-actuated inhaler. BAIs are the combination of all the benefits of a pMDI and DPI. It senses patient's inhalation through an actuator, then releases the medication automatically (Kondo et al. 2017).

Autohaler

It is by far the most easiest to use than a pMDI and also some DPIs. Children, adults and elder people all can effectively use it (Kondo et al. 2017).

1.3 Different types of Inhalers other than DPI

There are many types of inhalers all over the world other than dry powder inhaler. But dry powder inhalers are mostly acceptable in today's world as it doesn't need any propellant to be used in the formulation (de Boer et al. 2017).

Though dry powder inhaler is considered most convenient to use but before DPIs development, MDIs were used by most of the patients. MDIs can be used with spacers and in case of babies, with a baby mask. These additional devices increase the convenience for the patients but also have disadvantages. Then comes nebulizers which are also used by the Asthma patients as a mean of treatment like DPIs. It has its own suitability and difficulties to deal with like other inhalers (de Boer et al. 2017).

1.3.1 Pressurized Metered Dose Inhalers (pMDIs)

Pressurized metered dose inhalers are also called pump inhalers. They are most commonly used inhaler in the market. pMDIs are propellant-based and in the form of aerosol spray, they deliver precise amount of medication (aerosol spray) to the respiratory system. (Newman 2017).

Similar amount of dose is released every time as pMDIs provides reproducible doses every time on actuation. These inhalers do not depend upon the patient's inhalation to trigger the release of the drug (Newman 2017).

Pressurized metered dose inhalers require co-ordination between the actuation of the canister and inhalation of the dose. So, patient must inhale and press the canister at the same time to release the medication dose. Patients can have a dose counter with pMDIs by which they can easily know how many puffs are left in the device (Newman 2017).

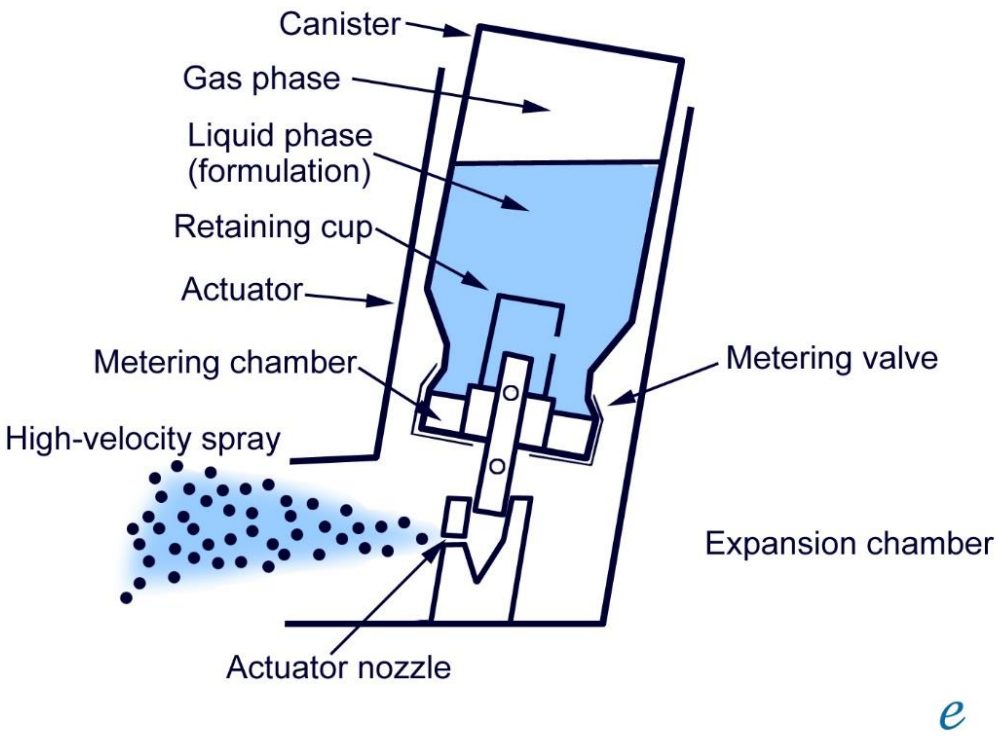

Figure 4: Metered Dose Inhaler (Newman 2017).

1.3.2 Zerostat VT Spacer

Zerostat VT spacer can be attached to the pMDI. After the pMDI's actuation, it holds the medication for a little while so that the spacer can help patients inhale the medications properly (Kondo et al. 2017).

1.3.3 Baby Mask

If children are unable to hold the Zerostat VT Spacer's mouthpiece appropriately, we can attach the baby mask to the Zerostat VT Spacer and then use the pMDI (Kondo et al. 2017).

With the help of the Baby Mask children can easily inhale the medicine, while breathing in & out through the mouth normally. It is also beneficial for those who have difficulty in maintaining a good lip seal on the mouth piece of the pMDI (Kondo et al. 2017).

The spacer and baby mask come preassembled in a Huf Puf Kit. As it is preassembled, it helps deliver the medication quickly in case of an emergency and saves time.

1.3.4 Nebulizers

Nebulizers' works by converting the liquid medication into suitable aerosol droplets, which are best suited for inhalation. Without any need of coordination, it delivers the medication rapidly and efficiently to the lungs in the form of a mist. Nebulizers are used during asthma attacks, in infants, children, elderly, critical, patient's unconscious patients, and for the patients who cannot use a pMDI or DPI efficiently (Newman 2017).

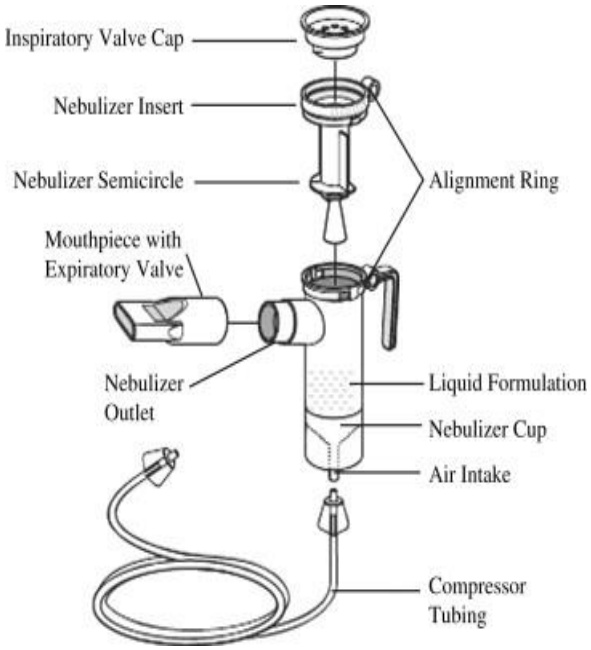

Figure 5: Nebulizer (Newman 2017).

1.4 Comparison between DPI and other Inhalers

Different types of inhalers have their own advantages and disadvantages based on the design of the device and formulation. The comparison between DPI, MDI and Nebulizer in terms of formulation, device, drug deposition and ease of use are given below:

Table 1: Comparison between DPI and other inhalers

	MDI	**DPI**	**Nebulizer**
Formulation	Propellant is used with the drug formulation which is in liquid form.	No propellant is used. Drug formulation can be used with carriers and also without carriers depending on the type of the drug particles and type of the formulation	Converts liquid medication into suitable droplets within the range one to five micrometers.
Device	Device used for metered dose inhalers has 1. Canister 2. Retaining Cup 3. Actuator 4. Metering Chamber 5. Metering valve 6. Expansion Chamber 7. Actuator Nozzle 8. Liquid Phase(Formulation)	Device design for DPI is different as the inhaler contains capsules filled with drug formulation.	It has: 1. Inspiratory Valve Cap 2. Mouthpiece 3. Alignment Ring 4. Nebulizer Cup 5. Compressor Tubing

	MDI	DPI	Nebulizer
	9. Gas Phase (Propellant)		
Ease of use	Not convenient to use by the patient.	A lot easier to use by the patient or patient friendly.	Patient friendly.
Oropharyngeal deposition	Higher Oropharyngeal deposition.	Less Oropharyngeal deposition and with the development of the formulations with the help of different technologies the amount of Oropharyngeal deposition is decreasing day by day.	Higher Oropharyngeal deposition.
Lung Deposition	It has lesser lung deposition compared to DPIs.	It has more lung deposition compared to MDIs and Nebulizers	It has lesser lung deposition than DPIs.

So we can see, in case of formulation, deposition and ease of use, DPIs are more advantageous than other types of inhalers.

Chapter 2

Technologies for DPI formulations with carrier:

2.1 Conventional Technologies

2.1.1 Milling

Size reduction of drug particles can be done either by mechanical size reduction or by controlled drug particle engineering techniques. In both ways the aim is to get fine sized drug particles which will be delivered easily to the targeted site of the respiratory tract.

Whether it is for the oral or pulmonary route, the particle has to be in a certain size so that maximum drugs can be delivered. In case of oral routes, drugs go through gastro intestinal fluids where the drugs have to be dissolved otherwise drugs would not go to the systemic circulation. For this reason, the drug particles have to be in a certain size to dissolute into the gastro intestinal fluid and enter the systemic circulation. For oral drug absorption the drug size can be within 10 micro meters. But lesser the size better will be the absorption and circulation in the body (Uday Raj et al. 2015; Arun et al. 2012).

The drug particles size for pulmonary route delivery must be within 1-5 micron meter. Drug particles between 1-5 micrometers are easy to deliver to the lung alveoli and from there to the systemic circulation. In addition to the size of the particles the agglomeration has much of importance.

If the drug particles get agglomerated then it forms different shapes of chunks which will not be appropriate to deliver to the lungs. These drug particles will settle down into the

oropharynx which is not desirable as it is a waste of the drug formulation and also the patient will not be getting the accurate drug effects too. Therefore, agglomeration is not desirable and drug particles should be as small as possible.

For the drug particles which don't reach its desired site and settle down in our mouth, we can use carriers for them. Carriers like lactose, sucrose are used mostly for drugs which are used for pulmonary delivery. The adhesive forces between drug and carrier particles has to be proper as it controls the dispersibility of drug particles in the inspired air which will affect the drug properties and how it will work in our body (Mossaad 2014).

For an ideal drug formulation, the drug particles has to have low agglomeration property, good flow property and also better batch to batch conformity. By milling we can achieve some of these properties but not all of them at once in one formulation and also not in a greater extent. But by controlled drug particle engineering techniques we can achieve these properties in drug formulations. Controlled drug particle engineering techniques are mainly spray drying, supercritical fluids technique etc.

Types of milling:

There are many types of milling techniques which has been in use for a long period of time (Wall 2015). For example Jet milling, Wet milling, Ball milling etc. It depends on the desired product that we will need.

In a general milling process milling is done by comminution of large particles into small particles.

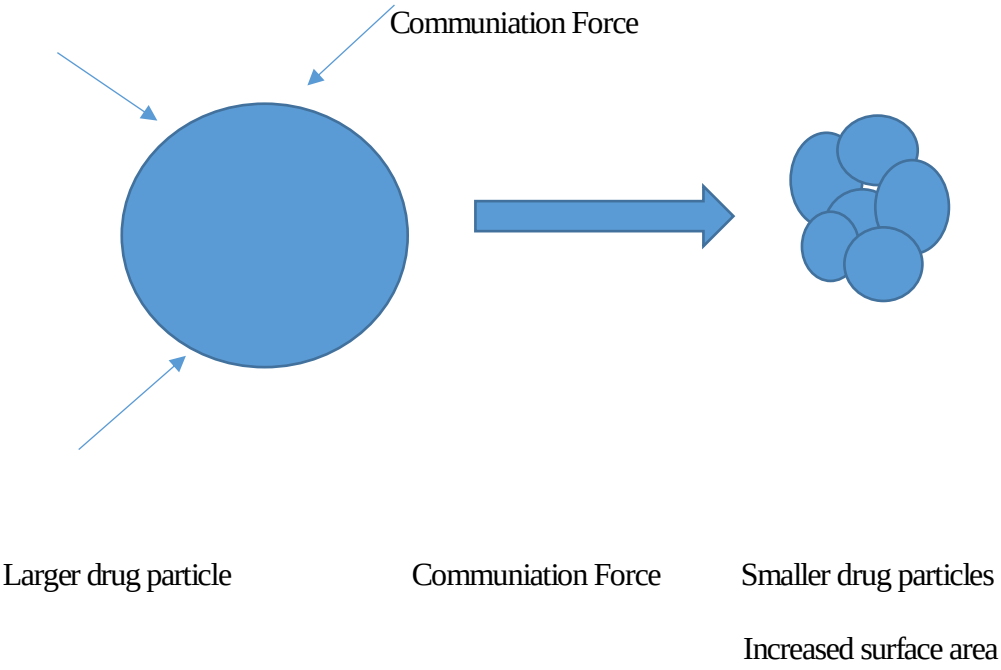

Figure 6: Milling process (in general) (Rasenack and Müller 2004).

2.1.2 Jet milling

This process is used for the reduction of drug particles within 10 micrometer. Many types of materials like solids of chemicals, pharmaceuticals, pigments, minerals and others like heat sensitive, corrosive and abrasive can be micronized in this technique (Rasenack and Müller 2004).

This process is operated in a compressed air, gas or high pressure super-heated steam. It doesn't have any moving parts and no additional heat is generated during its operation thus making it an ideal process for heat sensitive materials like waxy materials (Rasenack and Müller 2004).

Micronization takes place in a shallow, cylindrical chamber. There is nozzle designed in the chamber in the same peripheral distance so that high pressure air and steam can be injected easily to the materials inside the chamber. This high pressure air grinds the particles into smaller and discharged under the machine (Rasenack and Müller 2004).

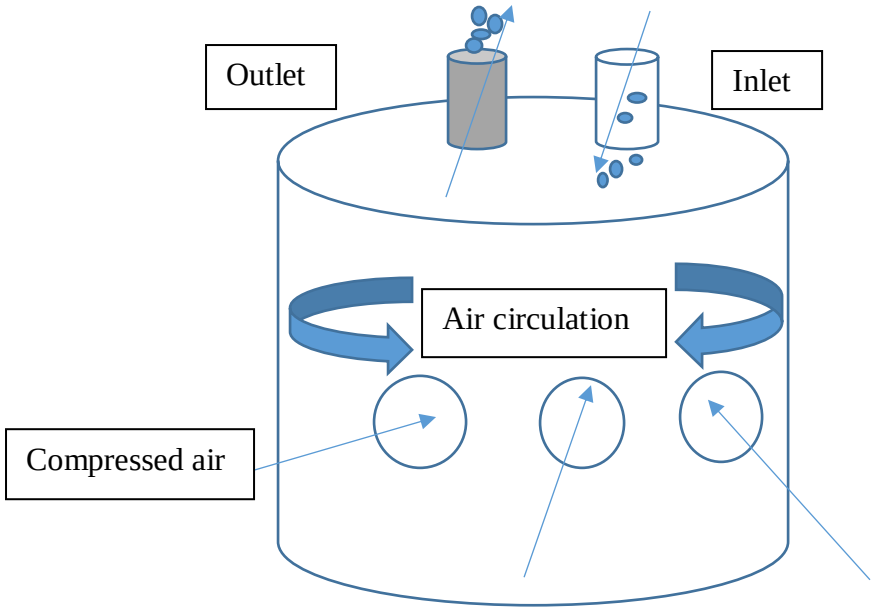

Figure 7: Air jet process (Rasenack and Müller 2004).

There are several factors, both operational and physical, which affects the fineness of the end product, such as feed rate, nozzle size, nozzle pressure, nozzle angle, airflow rate, feed particle size, chamber diameter and width, and product outlet diameter. All these factors have to be maintained on point to get desired products.

2.1.3 Ball milling

The tumbling ball milling has always been used for grinding larger particles into smaller particles. In a ball mill there are tumbling balls which will grind the bed of powder for an extended period of time to get the desired particle size and these balls are made of silicon carbide (Rasenack and Müller 2004).

Balls used in this technique provide a large amount of energy to crush the particles into smaller sizes. So we can see operational process of this technique is really easy to operate and we can get the desired result as well (Rasenack and Müller 2004).

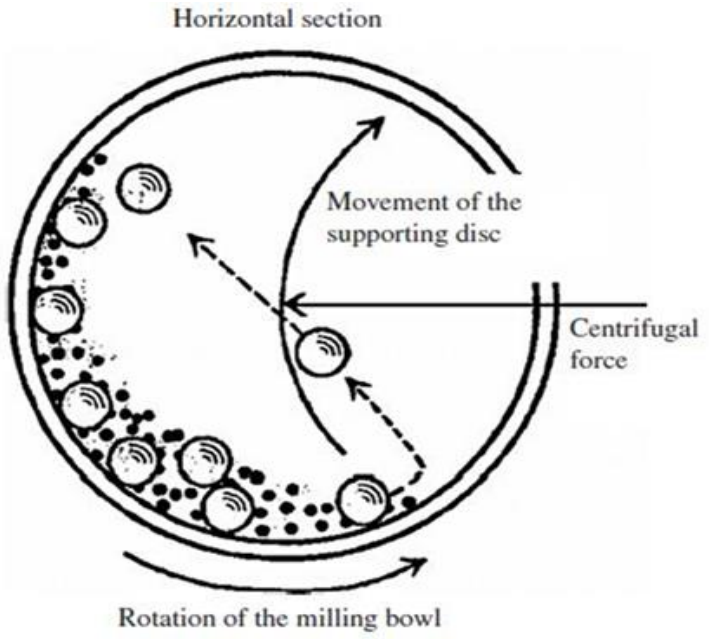

Figure 8: Ball milling (Rasenack and Müller 2004).

2.1.3 Wet milling

This process also reduces the size of the particles but this process is used with much care as this method needs liquid to process so partial dissolution occurs. Recrystallization and chemical instability can also occur easily which is not desired at all (Rasenack and Müller 2004). Meloxicam, an NSAID which has poor aqueous solubility so wet milling is used for reducing the particle size (Bartos et al. 2016)

Use of Milling

Dry-Powder Inhaler Formulation of Rifampicin for Alveolar Tuberculosis

For Alveolar Tuberculosis Rifampicin is being used along with lactose carrier. This combination is giving an improved targeted delivery from trachea to the alveoli. Rifampicin drug particles is reduced to smaller particles by milling and then mixed with coarse and fine lactose for maximum delivery of drug to the lungs (Persson 2006; Lau, Xie, and Ran 2016).

The micronized drug particles have a large surface area for which agglomeration is a common characteristic. So lactose is used to reduce agglomeration and for better flow. Drug

Particles of rifampicin within 1-5 micrometer goes to the alveoli, the main target place by passing pharynx, trachea, bronchus and bronchiole. If the particles are not in the right size then they will settle down in the mouth with the carrier and won't reach to the targeted site. So by milling we are getting micron sized drug particles which can go to targeted side much more easily. Like the process mentioned above milling is used for many drug particles which further is mixed with carriers to achieve the desired effect.

But milling is not an ideal process to get desired sized drug particles as it gives undesirable particle size, shape, decreased crystallinity and instability of the formulation (Vemavarapu et al. 2005). So it's safer to use controlled drug particle engineering techniques than milling as they have higher chances of giving desired particles.

2.2 Current Technologies

2.2.1 Spray Drying

Inhaled corticosteroids worked for inflammation, lung function improvement and also for asthma. That is why it has been recommended for asthma patients. Budesonide (BUD) is a corticosteroid type substance. It is one of the mostly utilized glucocorticoids and has a high ratio of topical anti-inflammatory to systemic activity (Daley-Yates and Baker 2001).

BUD lessens the airway hyper responsiveness, inflammatory cells and mediators present in the airways of the asthma patients. Thus, it reduces irritation and swelling of the airways, which makes breathing easier for the patient. This is how BUD works directly on lungs for patients with lung problems. So we can easily use budesonide for pulmonary administration (S. R. Naikwade et al. 2009).

By using spray drying technology we can form budesonide micro particles which will be microsphere and porous and will function in various ways in our body. By this technique we can have (S. R. Naikwade et al. 2009):

1. Controlled drug release
2. Specific drug targeting
3. Protection of incorporated active compounds against degradation
4. Lack of toxicity
5. Well tolerated polymers for example chitosan and gelatin

In current period, BUD has been selected as a potent corticosteroid with high glucocorticoid receptor affinity, extended tissue retention and preventing inflammatory indications like edema and vascular hyperpermeability (Cazzola 2006).

Spray dried budesonide particles give sustained drug release properties with excipient chitosan (Zatta et al. 2018) which is a useful excipient and can be used in various ways (Nep and Conway 2011; Shaji and Shaikh 2016).

Development of Budesonide formulation using spray drying

Before spray drying technique, budesonide dry powder formulation was prepared by sieving on laboratory scale. Twin stage impinger was used to evaluate the effect of excipient size on FPF of the formulation (S. Naikwade and Bajaj 2009).

Now we can use spray drying technique to form budesonide dry particles. We need chitosan as excipients to form sustained release budesonide micro particles. Chitosan has two types of monomers, chitin monomer and chitosan monomer. In the formulation the degree of deacetylation of chitosan affects overall charge density of the formulation (Nep and Conway 2011; Czechowska-Biskup et al. 2012; Dan and Shiguang 2005). Degree of deacetylation of chitosan is important as it indicates reactivity, solubility and viscosity of chitosan solution to be used in spray drying technique.

Microsphere formulation of Budesonide

Here, gelatin and chitosan which are natural polymers are used with budesonide to form microspheres. BUD and polymers are dissolved in methanol and water to prepare microspheres (S. Naikwade and Bajaj 2009).

The polymeric phase is mixed first using Ultra-Turrax at 13,000 rpm, in which methanolic phase is added slowly and then the solution was stirred to homogeneity and finally this solution is spray dried and microspheres are formed (S. Naikwade and Bajaj 2009).

Porous particle formulation of Budesonide

To form porous particle of budesonide,

BUD and polymers were spray dried in water and methanol (1:1) as 1.0% and 0.5% w/v, respectively like the formation of microsphere budesonide (S. R. Naikwade et al. 2009).

Here,

1. Solution containing BUD, polymer, a blowing agent is atomized in the drying chamber and then this atomized formulation is contacted with hot air stream (S. R. Naikwade et al. 2009).

2. Then blowing agent trapped in the droplet, decomposes with a higher temperature of the drying chamber and creates a void inside the particles (Baba and Nishida 2013; Ung 2016).

3. As the drying chamber temperature/ air stream temperature is very high, the temperature of the solvent in the solution increases until it evaporates (S. R. Naikwade et al. 2009).

4. Solvent at the surface (blowing agent) begins to evaporate causing solvent below the surface of droplet to diffuse to the surface (S. R. Naikwade et al. 2009).

5. The droplet by passing through the drying chamber forms a hollow particle (a promising material with low density, thermal insulation and distinct optical activity) (Yarragudi 2018).

6. The drug/polymer ratio is enhanced grounded on the percent of drug entrapment and release profile (S. R. Naikwade et al. 2009).

7. Finally, microspheres and porous particles obtained by spray drying are formulated with inhalable lactose (S. R. Naikwade et al. 2009).

Properties of the particles formed by Spray Drying Technique

The microspheres formed by this technique is found to be more effective than the formulation formed by conventional techniques and more micro particulate drug deposition in the lung has been found (S. R. Naikwade et al. 2009).

1. Evaluation of BUD DPI Formulations:

Table 2: Evaluation of budesonide DPI formulations (S. Naikwade and Bajaj 2009; S. R. Naikwade et al. 2009)

Formulation Type	**FPF (%)**	**Carr's index (%)**
Conventional drug particles/coarse lactose	31.8±0.22	46.3
Microspheres drug/ gelatin	29.3±0.01	12.5
Porous particles drug/ gelatin	12.2±0.02	25
Porous particles drug/ chitosan	46.8±0.09	26.7

From the table above it shows that, the conventional formulation which is formed by a traditional technique gives 46.3% flow ability which according to Carr's index, extremely poor flow ability thus will cause poor deposition in the lungs.

On the other hand formulations formed by spray drying technique gives 12.5%, 25% and 26.7% flow ability which according to Carr's index is good and slightly poor flow ability thus will provide better deposition in the lungs.

2. Formulations/ microspheres formed by the spray drying technique gave Hausner ratio between 1.2-1.7 which indicates good flow ability, as according to Hausner ratio the lesser the value (but it should be >2.0) better the flow ability (S. R. Naikwade et al. 2009).

3. Percent porosity for chitosan microspheres and porous particles formulation was found to be 30.76% and 26.66% respectively, which is better compared to conventional formulations having 6–20% porosity. Moisture content for all formulations was <1% (S. R. Naikwade et al. 2009).

So this technique is offering porous drug particles with good flow ability following better deposition in the lungs.

2.2.2 Anti-solvent Crystallization

Three things are necessary for drug delivery at the site of action. One is drug administration, second drug release and third is drug delivery (K. Jain 2008). In case of pulmonary delivery, inhalers are being used for many years for both local and systemic drug delivery for example asthma, COPD and also infections. Though high aerosolisation is a challenge as most of the drugs for pulmonary delivery which are available in the market has lower aerosolisation efficacy with fine particle fraction lower than ≤20% (Le et al. 2012; French, Edwards, and Niven 1996; Kaialy et al. 2012; Zhu 2013). For this reason, carriers are used in dry powder inhaler formulation as carriers increase the amount of drug availability in the lungs. In this regard the use of engineered carriers has been proven as a great possibility (Hassan and Lau 2011). For example: use of mannitol carrier having ethanol: water (Kaialy, Momin, et al. 2010) or acetone: water (Kaialy, Martin, et al. 2010), has been a great approach for more drug

transport to the lungs in case of DPI formulations. Researchers has found that by controlling the water content, physico-chemical and aerosol properties of mannitol carriers can be predetermined by controlled engineering.

Though at first, the focus was to have elongated carrier particles as this shape of carriers gives easy detachment between carriers and the drug particles but later it was proven that elongated carrier particles causes loss of drug amounts (Kaialy et al. 2011). Then, it was shown that carrier particles which have smaller sizes, increases the amount of respirable drug particles in lungs (Kaialy et al. 2011; Zhu 2013; Le et al. 2012).

Carrier particles with smaller size and rougher surface causes more deposition in the lungs compared to carriers with more elongated size and rougher surfaces (Kaialy and Nokhodchi 2013; Littringer et al. 2012).

Poor flow ability of the carriers were not a concern before but later on it has been confirmed that the more poor flow ability of the carriers the more loss of drugs were found and also fewer homogeneity of the drug contents was proven to be a problem for lesser drug deposition in the lungs (Kaialy, Martin, et al. 2010; Kaialy, Momin, et al. 2010).

Process

There is a process called anti solvent crystallization by which we can get predetermined lactose carriers for better drug deposition (Kaialy and Nokhodchi 2012).

In this process, lactose (carrier) used with salbutamol sulfate (drug content). For anti-solvent crystallization process absolute ethanol and 1-butanol is used. Engineered lactose carrier for salbutamol sulfate drug formulation is prepared by following steps (Kaialy and Nokhodchi 2012):

1. First, lactose is poured into deionized water and heat is given.
2. Then, stirring of the solution takes place.

3. After that, 30% and 60% lactose solution is made. From which 5 ml is given into 80ml of antisolvent media which is ethanol and butanol. The anti-solvent media has different volumes with different saturation (80:0, 60:20, 40:40, 20:60, 0:80).
4. After that, stirring is done and crystals are formed.
5. Then these crystals are collected and filtered under vacuum
6. Finally drying at 70 degree Celsius takes place and crystals are collected and put into vials.
7. Lactose particle size varies from 63-90 micrometer as they were sieved by 63 micrometer sieve and 90 micrometer sieve (Kaialy and Nokhodchi 2012). Because of ethanol:butanol antisolvent use, the crystals of lactose were whiter brighter and fluffier in appearance (Kaialy and Nokhodchi 2012).
8. In this process, the lactose crystals are prepared in narrow size distribution as they are sieved in sieves of 63 and 90 micrometers (Kaialy and Nokhodchi 2012).
9. The lower the bulk and tap density more drug deposition will occur after aerosolisation.

The result of in controlled anti solvent crystallization

Table 3: In controlled anti solvent crystallization result (Kaialy and Nokhodchi 2012)

Lactose product	**Bulk Density (g/mL)**	**Tap Density (g/mL)**
Commercial	0.62±0.01	0.76±0.00
Crystallised form of ethanol:butanol (80:0)	0.26±0.02	0.32±0.03
Crystallised form of ethanol:butanol (40:20)	0.19±0.02	0.25±0.03
Crystallised form of ethanol:butanol (20:60)	0.27±0.05	0.35±0.07

Lactose product	Bulk Density (g/mL)	Tap Density (g/mL)
Crystallised form of ethanol:butanol (60:20)	0.20±0.02	0.26±0.02
Crystallised form of ethanol:butanol (0:80)	0.38±0.17	0.46±0.18

By comparing the bulk and tap density of commercial lactose with antisolvent media containing different saturation, it is clear that the commercial lactose has more bulk and tap density than the antisolvent with different saturation in crystallized form. This result refers to more deposition after aerosolization.

It is evident that the more porous and round the lactose carriers the more flow ability and eventually more respirable rate of drug formulation in the lungs.

From the anti-solvent crystallization we get the following result:

Table 4: Antisolvent crystallization result (Kaialy and Nokhodchi 2012)

Lactose product	Roundness	Porosity (%)
Commercial	1.4±0.1	59.8±2.3
Crystallised form of ethanol:butanol (80:0)	2.1±0.4	83.6±1.1
Crystallised form of ethanol:butanol (0:80)	1.6±0.3	75.6±10.7

So, commercial lactose has lesser roundness and porosity than the crystallized lactose form. So crystallized lactose will give higher flow ability to the lungs.

It has been shown that the antisolvent media which has lower saturation has more yield.

Table 5: Antisolvent media saturation relation with yield (Kaialy and Nokhodchi 2012)

Lactose product	Yield (%)
Crystallised from of ethanol:butanol (60:20)	82.92%
Crystallised from of ethanol:butanol (40:20)	92.18%

So it is possible to have engineered lactose carriers with predetermined properties which not only makes the lactose whiter, brighter, fluffier, porous but gives higher yield as well.

2.2.3 Premix Membrane Homogenization

Premix Membrane Homogenization, a process where DPI formulation is developed with carriers to give desired effects.

Process

In this process,

First a coarse emulsion or premix is prepared by a continuous and dispersed phase mixing. This premix is carried out by magnetic stirring (Doan and Olivier 2009).

Then, premix goes through homogenization cycle by using a micro kit emulsification device equipped with Shirasu Porous Glass (SPG) membrane which has 5.9 micrometer pore size so that the emulsion can be prepared properly (Doan and Olivier 2009).

After that, emulsion then goes through magnetic stirring and collected by centrifugation (Doan and Olivier 2009).

Finally, by freeze drying microspheres are prepared (Doan and Olivier 2009).

According to the study we can easily get rifampicin loaded Poly Lactic-co-glycolic acid (PLGA) microspheres by the above process (Doan and Olivier 2009).

To prepare rifampicin loaded PLGA, the steps are given below:

(Doan and Olivier 2009)

1. For preparing premix, the continuous phase contains polyvinyl alcohol (PVA) solution saturated with ethyl acetate (EA) and the dispersed phase contains PLGA solution in EA. The rifampicin here is dissolved in the organic phase. Then the mixing takes place by magnetic stirring.

2. The mix then goes through homogenization cycles and SPG membrane and after that the emulsion is prepared and poured in a vessel.

3. Again magnetic stirring takes place and the emulsion is collected by centrifugation and finally washed with purified water and freeze dried to get rifampicin loaded PLGA microspheres.

4. For the content determination of rifampicin we can dissolve rifampicin loaded microsphere in dimethyl sulfoxide (DMSO).

Characterization of the particles that we get from premix membrane homogenization

1. Rifampicin loaded microspheres has size distribution around 1.72±0.16 micrometer which is preferable for dry powder inhaler formulation (Doan and Olivier 2009).

2. Mass median aerodynamic diameter (MMAD) is 2.6 micrometer which is good enough for good lung deposition (Doan and Olivier 2009).

3. This formulation has a release profile of 40% for rifampicin which has been shown linear in the curve for 4.5 days (Doan and Olivier 2009).

4. Respirable fraction is 54% where 35% is least to be accepted (Doan and Olivier 2009).

Chapter 3

Technologies for DPI formulation without carriers

3.1 Supercritical Fluid Technology

The gases and liquids which have their temperature and pressure above their critical points are called supercritical fluids (SF). Supercritical fluids have both the properties of liquids and fluids. So SF is highly compressible and particle formation is really easy by supercritical fluids near supercritical point. SF's density and solvation power can be controlled and designed as we want by controlling the temperature and pressure (York 1999).

For more than a century it was known that SF can dissolve nonvolatile solvents. In the 1970s, an interest was shown to SF methods for their cost saving reason in liquid extraction and distillation aspect (York 1999). Recently it is used in extraction processes mostly in decaffeination, tea, extraction of oils and flavors from different natural products (York 1999). In 1980 SF industrial application on purification of surfactants and pharmaceuticals, fractions of polymeric materials and chemical reactions and in polymerization was done. In the recent times the target is to prepare powdered pharmaceuticals with specific targeted properties like particle size (York 1999).

Types: There are many kinds of SF methods

1. Precipitation from superficial solutions
2. Precipitation from gas saturated solutions
3. Precipitation using SFs as non-solvents or anti solvents

1. Precipitation from superficial solutions

It basically involves dissolving of solute in supercritical fluid (SF) solvent then rapid expansion of SF solution across an orifice occurs which results in super saturation of the solute followed by homogeneous nucleation and particle formation (Matson et al. 1987). In rapid expansion of supercritical solution process reduction of SF density can occur by reducing solvent strength (Reverchon 1999). Solvent strength can be drastically reduced by reducing SF density (Matson et al. 1987). In this process, the required equipment needs a source of SF which then passes through an extractor to a restricted orifice positioned in a particle collection precipitation vessel which has low temperature and pressure than the extractor (York 1999). This rapid expansion of supercritical fluid (RESS) process can affect particle properties (York 1999) such as:

• Solubility of solute in organic solvent

• Insolubility of solute in SF

• Degree of expansion of organic solvent in SF

• Ratio between organic solvent/SF anti solvents

• Rate of addition of SF anti solvent

• Pressure of temperature conditions in precipitator

• Phase process path followed during particle nucleation

Inorganics, ceramics, organics and polymers can be processed by this process (York 1999). As well as microparticles and nanoparticles can be directly prepared by this single step operation (Reverchon 1999) .SF water is frequently used for inorganics and ceramics. SF-RESS has processed several pharmaceutical polymers including biodegradable polymers based on lactic acid (Debenedetti et al. 1993) and polyethylene glycol (York 1999). As

$SFCO_2$ nonpolar so nonpolar organics can be dissolved in $SFCO_2$ and so they are suitable candidates for SF-RESS processing. Examples are: lovastatin (Larson and King 1986), stigmasterol (Ohgaki et al. 1990), salicylic acid, theophylline (York 1999).

In this process super saturation increases while expansion causes extremely rapid nucleation and results in micron and sub-micron particles (Debenedetti et al. 1993). So particles formed by RESS have several ideal properties (Debenedetti et al. 1993) such as:

• Operates with relatively small quantities of organic solvent

• Molecular control of process

• Single step, scalable process for solvent-free final product

• Ability to control desired particle properties

• Suitable for a wide range of chemical types of therapeutic agents and formulation excipients

• Capability for preparing multi-component systems

In this process the key issue is the solubility of solutes of pharmaceutical materials like drug matrices in the selected SF solvent, typically used $SFCO_2$ (Snavely 1997). Though most pharmaceutical compounds shows solubility below 0.01 wt% under moderate processing conditions (Subramaniam, Rajewski, and Snavely 1997). However, predictive control of particle size and morphology are major challenges, as do processing and scale-up factors to eliminate particle aggregation and nozzle blockages caused by cooling effects on solution expansion (Subramaniam, Rajewski, and Snavely 1997).

2. Precipitation from gas saturated solutions

In this method, SF solvent dissolved in a solute that is molten and results in SF solution which pass by the orifice to cause a rapid expansion under suitable conditions (York 1999). This process is successful for processing micron sized particles of nifedipine and

polyethylene glycol 4000 (York 1999). The solute has to be molten in this process which limits this methods application in case of many pharmaceuticals and biological as the temperature of the solute has to be very high (York 1999).

3. Precipitation using SFs as non-solvents or anti solvents

In this method, SFs are used as non-solvents or anti solvents which uses the same method as solvent based crystallization process (York 1999).

SF has a high solubility in an organic solvent. So SFs are added in an organic solvent which leads to high expansion and because of that solvent density is deceased and a fall in solvent capacity occurs (Ohgaki et al. 1990). This increases super saturation following nucleation and crystallization and thus particle formation. Here typically $SFCO_2$ is used and it acts as an anti-solvent. This process is termed as gas anti solvent re-crystallization (York 1999).This process has gone through several modifications to improve control on final product characteristics (York 1999).

This SF-GAS process is performed as a batch process. This process influence particle properties (York 1999) such as:

• Solute solubility in organic solvent

• Solute insolubility in SF

• Degree of expansion of organic solvent in SF

• Organic solvent/SF anti solvent ratio

• Rate of addition of SF anti solvent

• Pressure of temperature conditions in precipitator

• Phase process path followed during particle nucleation

In these method drug particles gets nearly ideal characteristics.

Particle design for the drug delivery with SF method is given below

Particle formation by SF method is an emerging field. Several of pharmaceutical particles are getting processed by this method which is getting ideal drug particle design characteristics.

Formation Of micro-particles: Processes like high energy millings are not that efficient and causes surface and crystallographic damage and also provides highly charged particles (York 1999). These problems create more problems like batch variation, downstream processing difficulties and compromised stability (York 1999). But the single step SF process can form micro particles directly from drug solution which is indeed a very attractive alternative (York 1999). RESS process is capable of forming microparticles from drug solution. But there are some problems like nozzle blockage, limited solubility of pharmaceuticals etc (Mossaad 2014). By aerosol spray extraction system (AESS) used in supercritical fluid technology, the formation of micron sized particles of biopolymers is possible and drug loaded systems for modified release preparations using materials such as poly-L-lactic acid is also possible by AESS process (Miwa et al. 2016). A range of steroids for pulmonary delivery has been studied by AESS process. Supercritical anti solvent (SAS) process has unlike AESS process has been proved to make or produce micron sized particles of wide a range of materials like insulin, lysozyme, trypsin and methylprednisolone and hydrocortisone acetate (Miwa et al. 2016).

By using solution enhanced dispersion by supercritical fluids (SEDS) process a large number of materials has been prepared as micron and submicron like nicotinic acid, paracetamol, salbutamol sulfate and salmeterol, xinafolate (York 1999).

Solid state characteristics: The attention to the solid state characteristics of the drug particles is increasing as the polymorphs (crystal form of organic molecules) produced by conventional crystallization process is poor (Debenedetti et al. 1993). On top of that routine

crystallization and pretreatment operations lead to low level amorphous domains in materials which lead to unstable poor performed polymorphs (York 1999).

But in SEDS technique, pure forms of two salmeterol xinafolate polymorphs has been prepared by processing them in different regions of the supercritical phase with the same organic solvent (York 1999). Sample of the polymorphs has been shown chemical and physical stability and also no interconversion after five years (York 1999). By the same SF process a new polymorph of fruticasone propionate has been produced which has also shown stability and control over particle size and shape of formed particles (York 1999).

Purity: In SF processing methods $SGCO_2$ is used to purify materials post manufacture which gives satisfying purity and also not time consuming and costly either (York 1999).

Drug delivery systems: The use of SF processes in case of particle formation is now a reality. This has been used by various researchers in particular for drugs (Miwa et al. 2016). This SF process gives various benefits in case of smooth drug delivery to the specific region with the formation of micron sized drug particles (York 1999).

The benefits of SF processing have shown that micron-sized particles of indomethacin in combination with hydroxypropyl methylcellulose, ethyl cellulose and polyvinylpyrrolidone can be prepared by the SEDS process with a free flowing nature of the powder products (Miwa et al. 2016). These two features are often absent in products prepared by traditional precipitation techniques, which has limited the commercial application of conventional systems (York 1999).

SF-processed particles in both MDI and DPI drug delivery systems have reported satisfactory results. Favorable fine particle fractions have been observed for steroid formulations co prepared with 5% of lecithin during particle formation (York 1999).

A DPI formulation of salbutamol sulfate having increased fine particle fractions and targeted in vitro delivery has been demonstrated for SEDS-prepared powders when compared with micronized material which was satisfactory (Mossaad 2014). Similar effects have been observed for salmeterol xinafoate samples (Miwa et al. 2016).

So we can see, by Supercritical fluid technology, not only can we get good flow property, better FPF but also desired aerodynamic diameter for the particles which will further increase the rate of drug deposition in the lungs and will serve the purpose of engineering the drug particles for DPI formulations.

3.2 Spray freeze drying

In this technique, nanoparticle suspensions are sprayed into a stainless steel spray tower encased by a cooling jacket of liquid nitrogen through an atomizer nozzle (two fluid nozzles). After that, atomized particles are freeze and then lyophilized (freeze dried) so that the frozen solvent gets removed and leave the particles behind to form dry powder formulation (Nanotechnology, Houssam, and Hassan 2014; Date and Material 2017). Two fluid nozzles are used to increase the deposition into the lung.

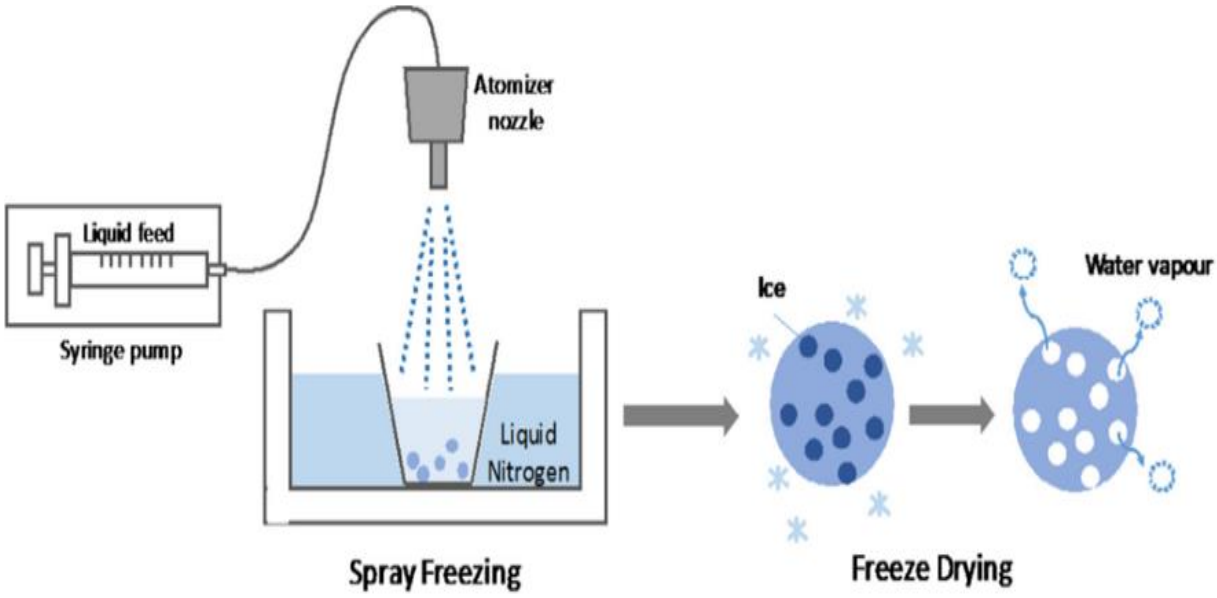

Figure 9: Spray Freeze Drying (Ali and Lamprecht 2014).

Comparison of the properties of Spray Dried NCM (Nano composite micro particles) and Spray freeze dried NCM (Nano composite micro particles) is given below:

Table 6: Comparison of the properties of spray dried nanocomposite microparticles (NMC) and spray freeze dried nanocomposite microparticles (NMC) (Ali and Lamprecht 2014)

	Spray Drying (SD) Poly (methyl) acrylate	**Spray Freeze Drying (SFD)** Poly (methyl) acrylate
Carr's compressibility index (%)	22.1±2.7	6.2± 1.9
Mass median aerodynamic diameter (MMAD)	3.3 ± 0.1	3.4± 0.3
Geometric Standard Deviation of the particle size distribution (GSD)	2.9 ± 0.1	3.1± 0.1

From the table above its evident that, nanoparticle from spray freeze drying are within 5-15% range according to Carr's index which indicates excellent flow ability of the particle where spray dried particle fall under good, fair or slightly poor category.

Then according to mass median aerodynamic diameter (MMAD), which is a parameter which indicates the deposition of inhaled drug particles, for SD and SFD are almost the same or slight difference exists.

Now for geometric standard deviation of the particle size distribution (GSD), which also is a parameter that indicates the deposition of inhaled drug particles, indicates that spray freeze dried prepared nanoparticles are better than the spray dried one.

So nanoparticles prepared by spray dried technique for dry powder inhaler to deliver into the pulmonary are greater than spray dried nanoparticles as they have better flow ability and deposition.

3.3 Sono- crystallization

Sono-crystallization is one of the most significant techniques to formulate dry powder inhaler formulation (Miwa et al., 2016). Ultrasound energy is applied in this process. Ultrasound energy used in this process, influence the nucleation and crystal growth of the particles in the crystallization process (Dhumal, Biradar, Paradkar, and York, 2009; Kim & Suslick, 2018).

In case of conventional anti solvent crystallization process, it gives poor mixing which results in heterogeneous growth of crystals and causes variation in particle size and morphological features (Kezia et al., 2016).

On the other hand, Sono crystallization which has ultrasound irradiation that induces acoustic streaming, micro streaming and highly localized temperature and pressure within the fluid which further induces primary nucleation and results in inhibition of agglomeration and formation of finite crystal size distribution (Kezia et al., 2016).

Advantages

1. Narrowing of metastable zone width (NMSZ) means crystallization can occur at lower saturation rate and also in higher temperature.

2. Nucleation is higher which leads to high small crystal formation.

3. Reduction of agglomeration.

4. Tailored crystal size (Kezia et al., 2016).

Types: Tailoring the crystal sizes can be done in three ways

- Continuous ultrasound produces many nuclei resulting in small crystals

- Initial ultrasound only produces finite nuclei which can be grown into large crystals
- Pulsed ultrasound gives tailored crystal size

Properties of particles in Sono-crystallization process

It has been found by comparing micronization process, spray drying process with sono-crystallization using salbutamol sulfate that,

FPF (Fine particle fraction %)

The fine particle fraction (FPF) of micronized salbutamol sulfate is 16.66%

The fine particle fraction (FPF) of spray dried aqueous salbutamol sulfate is 31.12%

The fine particle fraction (FPF) of sono-crystallized salbutamol sulfate is 44.21% (Dhumal et al., 2009).

Flow and stability

Sono-crystallization salbutamol sulfate was stable (without any change in crystallinity) Aerodynamic behavior for 3 months at 40 ◦C/75% (Dhumal et al., 2009)

Fine particle

Fine particles of salbutamol sulfate with a size distribution in a range of 2-5 micrometer, were successfully produced with elongated shape by sono-crystallization (Anuar et al., 2013; Hagedoorn, Hoppentocht, Hagedoorn, Frijlink, and Boer, 2014).

Comparison between the formulations of micronization formulation, sono-crystallization formulation and spray drying formulation of salbutamol sulfate:

Table 7: Comparison between the formulations of micronization formulation, sono-crystallization formulation and spray drying formulation of salbutamol sulfate (Dhumal et al., 2009)

	Micronized salbutamol sulfate (SS)	**Spray dried salbutamol sulfate (SDSS), fresh**	**Spray dried- sono-crystallized salbutamol sulfate (SD-SCSS), fresh**
FPF (%)	16.66%	31.12%	44.21%
Recovery (%)	89.18%	95.21%	98.33%
Emission (%)	59.04%	68.19%	74.63%

We can see from the comparison above and discussion that modern crystallization process (sono-crystallization) gives elongated shape crystals, good fine particle fraction and good emission rate which is mandatory for high formulation deposition in lungs.

3.4 Pulmosphere

Pulmosphere is a new technology which is being used to deliver drug particles to the pulmonary through trachea. This technique is an emulsion based spray drying technique which can give drug particles with desired properties.

Use of the technique : This technique is being used to prepare tobramycin drug particles for chronic pulmonary infection caused by Pseudomonas aeru-ginosa (Pa) and leads to cystic fibrosis, which is the reason of notable number of morbidity (Zemanick et al. 2015). The pseudomonas aeru-ginosa pathogen is the main reason of cystic fibrosis so the target of the antibiotic of the daily regimen is this pathogen (Kesser and Geller 2010; Kesser and Geller 2010). So aerosol drug delivery is the main effective way to deliver drugs to its targeted place easily and with more deposition of drug (Kesser and Geller 2010). Tobramycin and aztreonam are the drugs mostly used for the treatment as these drugs shows most of the efficacy in the treatment of cystic fibrosis (King et al. 2010; Sciences, City, and Canada

2011) and tobramycin inhalable solutions can be used not only for elders but also for children within six years and also this has been recommended by Cystic Fibrosis Foundation guidelines for treatment of chronic Pa infection. So we can easily say that it is safe.

Pulmosphere (Dry Powder Inhaler Technology)

Puolmosphere drug particles for DPI formulation are prepared by various steps to get the desired product (Schultz 2009; Vehring 2008). The steps are:

1. Feedstock preparation
2. Atomization
3. Drying
4. Collection

By high pressure homogenization, an emulsion based feedstock is prepared first. The emulsion will have oil droplets dispersed in water phase. The oil droplets are stabilized then by using monolayer of a phospholipid. Then the drug substance and excipients are dissolved in the continuous phase of the emulsion. Now this feedstock is atomized using twin fluid nozzle into a spray dryer. Then atomized droplets are dried and with continuation of the drying a shell is formed at the surface of each atomized droplet. Finally oil droplets are evaporated and leaves pore in each particle of drugs then they are collected from the airstream with a cyclone separator.

Components used in the pulmosphere technique to prepare tobramycin formulation for cystic fibrosis (Geller, Weers, and Heuerding 2011)

Table 8: Components to use in pulmosphere technique (Geller, Weers, and Heuerding 2011)

Components	**Use in the process**
Perflubron	Oil droplet dispersed in water
Distearoylphosphatidylcholine (DSPC)	Drug stabilizer

Components	Use in the process
Drug substance	Tobramycin
Excipients	Calcium Chloride
Water for irrigation	Process aid

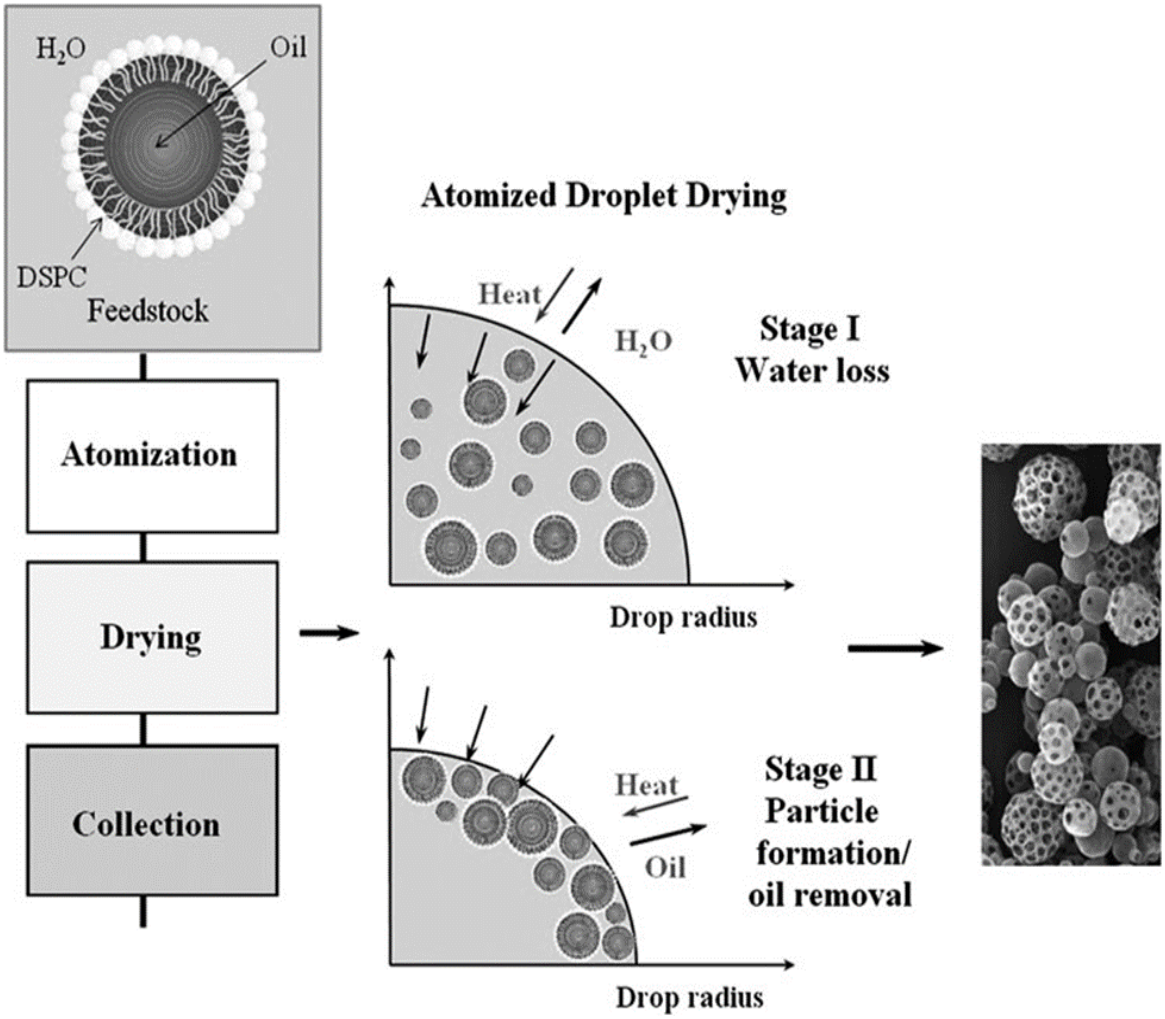

Figure 10: Pulmosphere work process (Geller, Weers, and Heuerding 2011).

DPI formulation prepared by pulmosphere technology provides 25gm drug on single actuation where formulation used in nebulizer gives 10-20 mg drug on single actuation. So it's clear that pulmosphere technology used for respiratory drug formulation delivers far more drug than nebulizer for tobramycin formulation (Geller, Weers, and Heuerding 2011).

Advantages of pulmosphere technique

1. Particles are highly porous with a sponge-like morphology
2. Gives particles spheroidal shape leading to less particle agglomeration
3. Fine particle deposition amount in the lung much more than the nebulizer technology
4. More convenient to use
5. Less time consuming as the technology is based on actuation
6. No cleaning before and after using

So we can easily say by further development in the future we can use this technology for more amount of deposition in the lung and which will give the desired effect in the body as needed not only for cystic fibrosis but for other pulmonary diseases as well.

3.5 Technosphere

Insulin is a hormone made in our body by an organ named pancreas which is essential to regulate the blood glucose level in our body. We suffer from diabetes if the glucose level increases (low amount of insulin in the body).

We can deliver insulin in our body by subcutaneous and intravenous routes. In fact they are the most common way to deliver insulin in our body. These routes are being used for many years now. But using subcutaneous injection provides too slow onset of action and long duration of action. After transferring insulin in body by subcutaneous injection, the peak serum level of the drug appears when the patient takes meal and meal is already digested. So what happens is, if the patient doesn't take any snack after taking insulin then his/her glucose level will be lowered than it needs to be and thus hypoglycemia can occur (Press 2016).

For this reason there has been many approaches over the years to develop a new route for delivering insulin more effectively and with less variability. The evolvement of fast acting recombinant insulin analogs which is intended to be improved in the near future is under observation (Mann and Steiner 2002). But there is also another route which has seen the light of success over the years and that is pulmonary route to deliver insulin in the diabetic patient's body.

Pulmonary route to deliver insulin has been a target for many years as lungs gives a very suitable and highly permeable access to the systemic circulation than other routes. Just the insulin molecules have to be within 1-5 micrometer to pass the respiratory tract with the airflow into the alveoli and also there is no risk of degradation of insulin by liver (Mossaad 2014).

Technosphere is a drug delivery system which is new and used for drug delivery in the lungs. It basically works with the liquid and dry powder insulin formulation which is used to prepare the appropriate insulin aerosol (Mann and Steiner 2002; Skyler et al. 2001). PTH, insulin and also glucagon can be used to deliver in the lungs by technosphere.

Drug delivery method of Technosphere

This system works by capturing and stabilizing peptides in small particles. In the process, it traps peptides and microencapsulated them for example insulin, parathyroid hormone (PTH) or glucagon and then next step is drying these small particles thus particle formation occurs. These drug particles are suitable vehicle for pulmonary transport (Mann and Steiner 2002).

After administration of drug (through technosphere) drug dissolves in neutral PH of deep lungs then goes to the systemic circulation where rapid and efficient absorption of peptides happens. Finally excretion within hours after administration takes place (Mann and Steiner 2002).

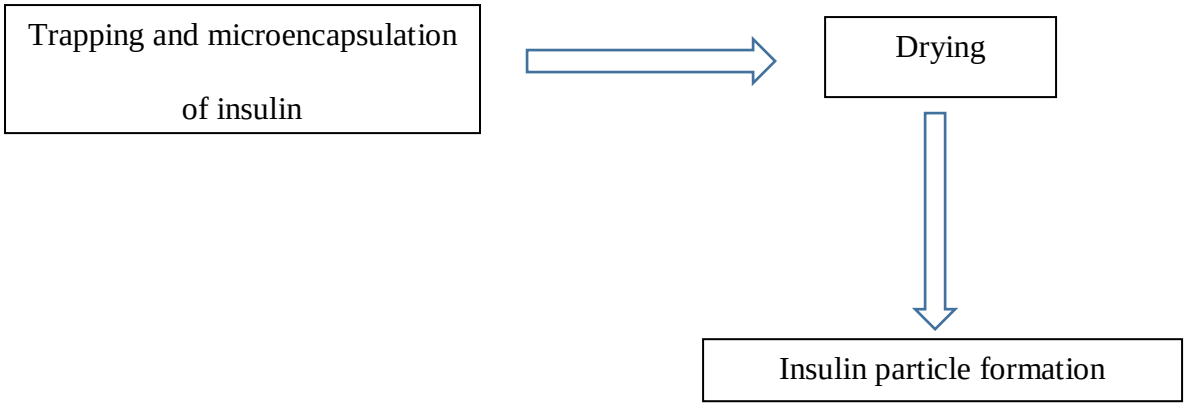

Figure 11: Insulin particle formation by technosphere to deliver through pulmonary route (Pfützner, Mann, and Steiner 2002)

Tests and Results

- Firstly a test using euglycemic clamp technique has been done where not only pulmonary but also subcutaneous and intravenous routes was used to find out the efficacy comparison between these three drug administration routes. In this test, 100 International Units (IU) has been used for newly formulated formulation, delivered by new technology technosphere and 10 IU and 5 IU subcutaneously injected and intravenously injected human insulin was used. A table containing the results is given below

Table 9: Comparison between pulmonary route by technosphere technique, subcutaneous route by injection and intravenous route by injection (Pfützner, Mann, and Steiner 2002)

Route of administration	**Tmax**
Pulmonary route by technosphere technique	13±4 min
Subcutaneous route by injection	121±74 min
Intravenous route by injection	9±4 min

We can see that the time to reach the highest plasma concentration for drug is higher in case of intravenous route and pulmonary route. But intravenous route has other complications

which pulmonary route doesn't. It can be observed that with less variability the faster onset of action is given by pulmonary route.

- After three hours of administration the amount of drug availability in the body by pulmonary route is 26±12% and after six hours it is 6±8%. Moreover there was no severe complications and problems found in the volunteer's body and the little variability that has been shown is lower than the variability produced by subcutaneous route (Heinemann, Traut, and Heise 1997).

Advantage over other technologies

1. This technique needs a little force to de agglomerate the drug particles so less drug agglomeration occurs.
2. Gives higher bioavailability.
3. Faster onset of action.
4. Many drugs have shown reliability and stability in this drug delivery system.
5. It has characteristics which can be used for not only elders but also children's both normal and compromised pulmonary systems (Hank 1999).

This technique is still under observation but so far has shown a lot of efficiency over other routes in case of insulin drug delivery. If further research can show better tolerability and efficacy with stability profile this drug delivery technique will be an attractive method to deliver insulin and other peptide drugs in the body.

3.6 High Gravity Controlled Anti solvent Precipitations

Hence there is another technique which is high gravity controlled antisolvent precipitation. This technique gives narrow size distribution of the particles (Barhoum et al. 2014) and recently this technique is also used in the formulation of nanoparticles (Haranas, Gkigkitzis,

and Alexiou 2014). At present it is being used in the production of salbutamol sulfate formulation with spray drying technique. The process is being discussed in the following section:

Process

In this process, salbutamol sulfate which is a B2 adrenoceptor stimulant (usually used in asthma treatment) have been formulated into amorphous powder respectively by high gravity controlled precipitation and dry mixing (Chiou et al. 2007).

The process occurs in a modified high gravity controlled precipitator (HGCP). In this modified HGCP, there is a rotating packed bed (RPB) reactor in which two liquid streams are served into by two distributors and then mixing takes place in the center of packed bed. The mixing takes place because of a centrifugal force inside of the reactor and this centrifugal force also is the reason of the gravitational force inside the reactor. This gravitational force leads the mixing to flow through packing before the mixing leaves the reactor. The RPB reactor has a port on its top to insert reagent inside the reactor or this port can also be used to clean the reactor (Chiou et al. 2007).

Salbutamol sulfate is introduced in this process through the second liquid inlet into the RPB reactor and through the first liquid inlet isopropyl alcohol (IPA) is introduced as an antisolvent. Then rapid circulation occurs inside the RPB reactor through the peristaltic pump. The mixing occurs at four different running times as the frequency of the RPB set at 50 Hz, which is the highest frequency to run the process. After each run ends, salbutamol sulfate is collected from the outlet of RPB. Then spray drying of the suspension of precipitated salbutamol sulfate takes place. After drying, the spray dried powders are collected in a container and then storing takes place with the help of silica gel (Chiou et al. 2007).

HGCP process gives particles of salbutamol sulfate which have elongated shape with a length of 1-10 micrometer which is not ideal for dry powder inhaler formulation development. So, spray drying takes place to break the elongated powder particles into very small fragments like 4.4 micrometer of salbutamol sulfate powder particles which is accurate for dry powder inhaler formulation but the particles will be amorphous and hygroscopic in nature and is proven to recrystallize at 70% humidity though the aerosol performance and deposition in the lungs of these spray dried particles are satisfactory (Chiou et al. 2007).

Aerodynamic properties of salbutamol sulfate powders dispersed at 60 L/min with aeroliser is given below

Table 10: Aerodynamic properties of Salbutamol Sulfate powders dispersed at 60 L/min with aeroliser (Chiou et al. 2007)

Sample	**FPF (%)**	**Dispersibility (%)**	**Capsule and device retention (%)**	**Impaction loss (%)**
Salbutamol sulfate formulation after HGCP process and spray drying	54.5% (±4.9)	71.3% (±10.0)	20.2 (±1.0)	7.3 (±0.5)

Advantages & Disadvantage of high gravity controlled anti solvent precipitations:

Table 11: Advantages & Disadvantage of high gravity controlled anti solvent precipitations (Chiou et al. 2007)

Advantages	**Disadvantages**
Gives good FPF	Amorphous powder particles
Good lung deposition	Hygroscopic nature that's why stored with silica
Less capsule and device retention	Recrystallization can occur at 70% relative

Advantages	Disadvantages
	humidity

HGCP and spray drying are producing powder formulations which are amorphous in nature but still has a satisfactory fine particle fraction (more than 50%) where we need minimum 35% of FPF to get into our lungs for a better result. Also dispersion rate, capsule and device retention rate and impaction loss rate are satisfactory to get a good deposition in lungs.

Chapter 4

Discussion

4.1 DPI formulations with carrier

Observation of DPI formulations with carrier is given in the following section

The characteristics of the drug particles depends on the type of milling used as there are different types of milling techniques giving different types of drug particle properties. For example jet milling gives drug particles of 10 micrometers by grinding the formulation inside a high pressure air chamber (Rasenack and Müller 2004). As this process is operated in a compressed air, gas or high pressure super-heated steam and no additional heat is generated when the operation is going on so it is an ideal process for the waxy type materials. Next in ball milling we have tumbling balls made of silicon carbide which will grind the bed of powder for an extended period of time to get the desired particle size (Rasenack and Müller 2004). Then, in wet milling we have to be very careful as this method needs liquid to process so partial dissolution occurs (Rasenack and Müller 2004). Moreover targeted delivery system for alveolar tuberculosis, DPI formulation of rifampicin is used which first goes through milling process to reduce into smaller size and then mixed with coarse and fine lactose for maximum delivery of drug to the lungs (Persson 2006). If the rifampicin drug particles are not in the right size then they will sediment in the mouth with the carrier and won't reach to the targeted side (Lau, Xie, and Ran 2016). So by milling we are getting micron sized drug particles which can go to targeted side much more easily. Furthermore, milling is a very conventional process and gives drug particles which have undesirable particle size, shape, decreased crystallinity and instability of the formulation (Vemavarapu et al. 2005) So milling

is not a very ideal process to use for the production of DPI drug formulation so it's safer to use controlled drug particle engineering techniques than milling as they have higher chances of giving desired particles (Rasenack and Müller 2004).

We can make a budesonide (BUD) formulation by spray drying as budesonide works directly on lungs for patients with lung problems. In this process sieving is done before going for the spray drying technique to reduce BUD drug particles (Naikwade et al. 2009). Then chitosan is needed as excipients to form sustained release budesonide micro particles. Solution containing BUD, polymer (Chitosan), a blowing agent is atomized in the drying chamber and then this atomized formulation is contacted with hot air stream. After that, blowing agent trapped in the droplet, decomposes with a higher temperature of the drying chamber and creates a void inside the particles and later on passing other stages porous budesonide drug particles are formed which have higher fine particle fraction (FPF) and satisfactory flow ability with good drug deposition. We can observe that from this technology we can get, controlled drug release, micro and porous particles with excellent Carr's Index (CI). We also can do drug targeting using this technology and not to mention we can reduce the toxicity of drug in the body as well. So it is visible that this technology has lots to give to formulate an impeccable DPI formulation (Naikwade et al. 2009).

Anti-Solvent Crystallization offers predetermined lactose carriers for better drug deposition. Lactose solution is made by pouring into deionized water with heating and stirring. Then anti-solvent media with different volumes and with different saturation is taken for further stirring and crystals are formed. These crystals are collected and filtered under vacuum. Finally drying at 70 degree Celsius takes place and crystals are collected and put into vials. Lactose carriers prepared by controlled anti solvent crystallization is whiter brighter and fluffier in appearance because of ethanol: butanol antisolvent use. Then they have narrow size distribution as sieved by 63 micrometer sieve and 90 micrometer sieve, lower bulk and tap

density with more drug deposition and porosity (75.6±10.7%) with excellent flow ability (Kaialy and Nokhodchi 2012).

In Premix Membrane Homogenization, we can easily get rifampicin loaded Poly Lactic-co-glycolic acid (PLGA) microspheres (Doan and Olivier 2009). To prepare rifampicin loaded PLGA microspheres, premix continuous phase contains polyvinyl alcohol (PVA) solution saturated with ethyl acetate (EA) and the dispersed phase contains PLGA solution in EA. The rifampicin here is dissolved in the organic phase. Then the mixing takes place by magnetic stirring. The mix then goes through homogenization cycles and shirasu porous membrane (SPG) membrane which has 5.9 micrometers pore size so that the emulsion can be prepared properly and after that the emulsion is prepared and poured in a vessel. Then again magnetic stirring takes place and the emulsion is collected by centrifugation and finally washed with purified water and freeze dried to get rifampicin loaded PLGA microspheres. So this technology provides FPF more than 50% because of the magnetic stirring before and after SPG membrane passing of the emulsion and then freeze drying the formulation before final collection. Moreover it gives higher flow ability as the aerodynamic diameter remains within range because the emulsion goes through 5.9 micrometer SPG membrane and then subsequently stirring, centrifugation takes place. Mass median aerodynamic diameter (MMAD) value that we get from the formulations is within 2.6 which is satisfactory to give a good deposition in the lungs (Doan and Olivier 2009).

So we can say formulations with carrier's offers a satisfactory result in case of flow ability of the particles and also the FPF amount is higher than the conventional technologies used before like milling. These processes like spray drying, Anti-solvent crystallization and Premix membrane homogenization are giving excellent flow ability according to Carr's index (CI), desired MMAD, higher FPF percentage and finally more drug deposition.

4.2 DPI formulations without carrier

Observation of DPI formulations without carrier is given in the following section

In the recent times supercritical fluid (SCF) technology is being used to prepare powdered pharmaceuticals with specific targeted properties like particle size. As supercritical fluids (SF) have both the properties of liquids and fluids it is highly compressible and particle formation near supercritical point is really easy. SF's density and solvation power can be controlled and designed as we want by controlling the temperature and pressure. This technology has many types of process to formulate desired DPIs like precipitation from superficial solutions, precipitation from gas saturated solutions and precipitation using SFs as non-solvents or anti solvents. In precipitation from superficial solutions, dissolving of solute in SF solvent then rapid expansion of SF solution across an orifice occurs which results in super saturation of the solute and followed by homogeneous nucleation results in micron sub-micron particles. So microparticles and nanoparticles can be directly prepared by this single step operation. Inorganics, ceramics, organics and polymers can be processed by this process. This process has processed several pharmaceutical polymers including biodegradable polymers based on lactic acid and polyethylene glycol. Also it has ability to control desired particle properties and suitable for a wide range of chemical types of therapeutic agents and formulation excipients. After that, in precipitation from gas saturated solutions process is successful for processing micron sized particles of nifedipine and polyethylene glycol 4000 as SF solution which by the orifice goes to the chamber and cause a rapid expansion under suitable conditions (Doan and Olivier 2009). Then in precipitation using SFs as non-solvents or anti solvents method, SFs are added in an organic solvent which leads to high expansion and because of that solvent density is deceased and a fall in solvent capacity occurs. This increases super saturation following nucleation and crystallization and thus particle

formation. These particles formed , gives solid state characteristics for example pure forms of two salmeterol xinafolate polymorphs has been prepared by processing them in different regions of the supercritical phase with the same organic solvent. Sample of the polymorphs have shown chemical and physical stability and also no interconversion after five years. Then in SF processing methods SGCO2 is used to purify materials post manufacture and also not time consuming and costly either. Also gives good drug delivery to the targeted site because of the formation of micron and sub-micron sized particles (Doan and Olivier 2009).

Spray freeze drying technology offers a formation of nanoparticles for higher deposition in the lungs. In this process nanoparticle suspensions are sprayed into a stainless steel spray tower encased by a cooling jacket of liquid nitrogen through an atomizer nozzle (two fluid nozzle). Then atomized particles are frozen and then lyophilized (freeze dried) so that the frozen solvent gets removed and leave the particles behind to form dry powder formulation. Two fluid nozzles are used which result in increased deposition into the lung. Drug particles formed by this method also gives excellent flow ability according to the CI (Ali and Lamprecht 2014).

Sono-crystallization which has ultrasound irradiation that induces acoustic streaming, micro streaming and highly localized temperature and pressure within the fluid which further induces primary nucleation and results in inhibition of agglomeration and formation of finite crystal size distribution. This one gives more than 40% FPF, tailored drug particles and by comparing the formulations of micronization formulation, sono-crystallization formulation and spray drying formulation of salbutamol sulfate it has been seen that modern crystallization process (sono-crystallization) gives elongated shapes crystals, good fine particle fraction and good emission rate than the other ones but the performance on storage is quite poor (Guenette et al. 2009).

Pulmosphere is a new technology which is an emulsion based spray drying technique that can give drug particles with desired properties. The emulsion will have oil droplets dispersed in water phase. The oil droplets are stabilized by using monolayer of a phospholipid. Then the drug substance and excipients are dissolved in the continuous phase of the emulsion. Now this feedstock is atomized using twin fluid nozzle into a spray dryer. Then atomized droplets are dried and with continuation of the drying a shell is formed at the surface of each atomized droplets. Finally oil droplets are evaporated and leaves pore in each drug particle and because of this pore formation particles formed by this process are highly porous with a sponge-like morphology. The particles also have spheroidal shape leading to excellent flow ability and less particle agglomeration and not to mention the FPF percentage is also good leading to high drug deposition (Geller, Weers, and Heuerding 2011).

Technosphere is a new system, used for drug delivery in the lungs. It works with the liquid and dry powder insulin formulation which is used to prepare the appropriate insulin aerosol. Parathyroid hormone (PTH), insulin and also glucagon can be used to deliver in the lungs by technosphere. Formulation formed by this technology gives high plasma concentration in lesser amount of time with less variability and no severe complications compared to subcutaneous route and intravenous route by injection. Then in this technique after entrapping of the peptides (insulin), microencapsulation occurs and then drying takes place which results in particles with less agglomeration tendency. For this reason this technology can give good flow ability of the drug particles which leads to higher drug deposition. Moreover, ensures fast on set of action and more stability and also the formulation have characteristics which can be used for not only elders but also children's both normal and compromised pulmonary systems. But this technique is still under observation but so far has shown a lot of efficiency over other routes in case of insulin drug delivery. If further research can show better tolerability and efficacy with stability profile this drug delivery technique

will be an attractive method to deliver insulin and other peptide drugs in the body (Pfützner, Mann, and Steiner 2002).

In high gravity controlled anti-solvent precipitation process, formulation mixing occurs in a reactor with peristaltic pump and after mixing formulation is collected from the outlet. But the formulation that we get, gives drug particles with elongated shape and a length of 1-10 micrometer. For this reason, spray drying takes place and breaks the elongated powder particles into very small fragments like 4.4 micrometer which is precise in terms of aerodynamic diameter of drug particles. For example high gravity controlled anti-solvent precipitation used in salbutamol sulfate formulation along with spray drying gives more than 50% FPF, with a dispersion rate more than 71.3% which ensures good flow ability and higher drug deposition as capsule and device retention is less than 21% but there are flaws too like the particles will be amorphous and hygroscopic in nature and is proven to recrystallize at 70% humidity (Chiou et al. 2007).

From the above discussion it can be said that many advanced technologies are being used for the formulations without carriers like pulmosphere, technosphere. All these progressive techniques are showing satisfactory results. For example, HGCP gives more than 50% FPF which is excellent. Then technosphere is delivering insulin in our body through pulmonary route which is phenomenal, pulmosphere is giving spheroidal shaped porous particles with excellent flow ability, sono-crystallization gives more than 40% FPF, SCF is providing micro and submicron particles with purity and stability and spray freeze drying is giving excellent flow ability to the drug particles for better drug absorption. This proves that the technology for DPI formulation without carriers is getting advanced with time and with more research these technologies will be able to provide useful results in the near future.

From the discussion above it implicates that, every technology has its good sides but not any of the technologies are perfect and giving 100% FPF, highest flow ability to reach 100% drug deposition in lungs but surely these technologies are giving much more drug deposition, lesser drug loss and toxicity in the body than the conventional ones. To sum up it can be said that DPI formulation technology has come so far in case of development and giving higher drug effect in the body but there is a lot more way to further advancement and development.

4.3 Comparison of each technology regarding their major properties as perfect DPI formulation

Comparison of each technology from above discussion regarding their major properties is given in the following section

Table 12: Comparison of each technology regarding their major properties as perfect DPI formulation

Name of the technology	Fine Particle Fraction	Flow ability	Aerodynamic Diameter	Surface Texture	Drug Deposition	References
Milling	Fine particle fraction increases with the use of carriers in milling	Normally milling gives low flow ability but it increases with the use of carries	Meets the minimum requirement to give a good flow ability as carrier is used	Surface texture is not satisfactory because of the mechanical forces of milling process	Drug deposition is found low as surface texture is not satisfactory	(Rasenack and Müller 2004).
Spray Drying	FPF of Porous particles of drug/ Chitosan is 46.8±0.09% which is adequate	According to Carr's Index 12.5 is the flow property which is satisfying	Meets the minimum requirement to give a good flow	Coarse in case of carriers	Satisfactory	(Naikwade et al. 2009).

Name of the technology	Fine Particle Fraction	Flow ability	Aerodynamic Diameter	Surface Texture	Drug Deposition	References
			ability as carrier is used			
Anti- Solvent Crystallization	Adequate	Excellent as porosity of the particles are more than75%	Meets the minimum requirement to give a good enough flow ability as carrier is used	Coarse in case of carriers	High	(Kaialy and Nokhodchi 2012).
Premix Membrane Homogenization	54%	Excellent	Meets the minimum requirement to give a good flow ability as carrier is	Coarse in case of carriers	MMAD is 2.6 which defined it's good deposition	(Doan and Olivier 2009).

Name of the technology	Fine Particle Fraction	Flow ability	Aerodynamic Diameter	Surface Texture	Drug Deposition	References
			used			
Supercritical Fluid Technology	Favorable	Free Flowing	Within one to five micrometers	Smooth texture of the particles	High	(Doan and Olivier 2009).
Spray Freeze Drying	Not mentioned but enough considering the excellent flow property of the particles	Excellent	Within one to five micrometers	Smooth texture of the particles	High	(Ali and Lamprecht 2014).
Sono Crystallization	44.21% in case of Salbutamol sulfate which can be mentioned as satisfactory	Good	Within one to five micrometers	Smooth texture of the particles	High	(Guenette et al. 2009).
Pulmosphere	Porous particles are formed	Excellent	Within one to five micrometers	Smooth surface texture	High	(Geller, Weers, and Heuerding

Name of the technology	Fine Particle Fraction	Flow ability	Aerodynamic Diameter	Surface Texture	Drug Deposition	References
						2011).
Technosphere	Not mentioned in digit but enough considering the properties of the particles such as less agglomeration, more stability, high availability and fast action	Good	Within one to five micrometers	Smooth texture of the particles	Good Enough	(Pfützner, Mann, and Steiner 2002).
High Gravity Controlled Antisolvent Precipitation	54.5% (±4.9)%	Good	Within one to five micrometers	Smooth texture of the particles	High	(Chiou et al. 2007).

Chapter 5

Conclusion

Dry Powder Inhaler is the most widely used among all the inhalers (MDIs, Nebulizers) in the market today. They are easily usable, cost effective and provide higher effect in the body. Higher drug deposition in the respiratory system is the major goal of all the inhalers. DPIs are ahead than other drug devices in this regarded. Most of the DPIs available in the market, used to give minimum 20% of drug deposition in the lungs. But in last 10-15 years the scenario has changed enormously. With the help of advanced technologies, formulation efficiency has been improved. Advanced technologies for the formulations with carriers (spray drying, anti-solvent crystallization) and without carriers (pulmosphere, technosphere, sonocrystallization), ensuring drug deposition from 35% to more than 50% in some cases. This is occurring as these progressive processes are providing aerodynamic diameter within the range of 1-5 micrometers with excellent flow property, FPF with higher percentages and specific surface texture for specific drug formulation such as for with carrier formulation, carrier's surface texture is rougher for drug particle adhesion, but for without carrier formulations, surface texture is smoother for non-agglomeration. Though there are many methods for DPI's to give higher deposition in lower time with higher effect but each of these methods has their own weaknesses alongside with their benefits such as, high gravity controlled anti-solvent precipitation gives elongated particles first but then another technology called spray drying is used to form smaller drug particles otherwise this formulation will not be effective. Using two methods for drug formulation increases the cost of the product. Though the drug formulation is proficient but the device is not working properly then it can be a huge

problem. Like formulation the device plays a significant role in case of drug deposition in the respiratory system. So both device and formulation must be up to the mark. But there is another factor to be concerned about which is called behavioral factor. If the patient cannot use the device correctly then most of the drugs will not be deposited in the lungs and deposition percentage in the lungs will be so low that no effect will be provided in the body. Also the patient has to be adhered to the regimen to get desired result. Finally we can say that no technology is near to perfect to give a perfect drug deposition and not just the technology should be blamed but the device and the patient who is using it should be instructed accordingly and more research are needed to reach a technology which can give perfect drug deposition in the lungs with less amount time and with highest efficiency.

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