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Review Article

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PRONIOSOME: A PROMISING PULMONARY DRUG DELIVERY SYSTEM

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ABSTRACT

Pulmonary drug delivery is primarily used to treat conditions of airways, delivering locally acting drugs directly to their site of action. Delivery of anti-asthmatic and other locally acting drugs directly to their site of action reduces the dose needed to produce a pharmacological effect, while the low concentrations in the systemic circulation may also reduce side effects.Vesicular drug delivery systems have gained wide attention in the field of nanotechnology. Among them proniosomes become the superior over other vesicular carriers. Proniosomes are dry formulations of water soluble nonionic surfactant coated carrier system which immediately forms niosomes upon hydration. They have the capability to overcome the instability problems associated with niosomes and liposomes and have the potential to improve solubility, bioavailability, and absorption of various drugs. This review discusses about the use of proniosomes in pulmonary targeting of drugs for better therapeutic efficacy. Moreover, this review demonstrates critical appraisal of the literature for proniosomes and explains delivering drugs via pulmonary route.

KEYWORDS: Niosomes, proniosomes, pulmonary route.

INTRODUCTION

Pulmonary drug delivery is primarily used to treat conditions of airways, delivering locally acting drugs directly to their site of action. Delivery of anti-asthmatic and other locally acting drugs directly to their site of action reduces the dose needed to produce a pharmacological effect, while the low concentrations in the systemic circulation may also reduce side effects.

The lung may additionally be employed as a route for delivery of drugs in to the systemic circulation, and onward to an effect site located elsewhere in the body. A product containing ergotamine tartrate is available as an aerosolized dosage inhaler for the treatment of migraine. Volatile anesthetics, including, for the systemic delivery of peptides and other molecules which are not absorbed through the GIT has also been explored. Pulmonary drug delivery could be used for both local and systemic effects (Table No: I).

Table No:I- List of Pulmonary drug delivery drugs.

Drug type	Disease	Examples
b_2-adrenoceptor agonist	asthma, COPD	Salbutamol, terbutaline, Fenoterol, salmeterol
Corticosteroids	asthma, COPD	Budesonide, beclomethason
Anticholinergics	asthma, COPD	Ipratropium bromide
anti-inflammatory	Asthma	nedocromil, cromoglycate
Mucolytics	CF	N-acetylcysteine
Antibiotics	Respiratory infections (CF, AIDS)	Pentamidine, aminoglycosides e.g. tobramycin

The administration of drug via pulmonary route exhibit several barrier for delivering the drug to the desired site of action. The first barrier which is encountered before the drug can reach its site of action is the mucus, present as a viscoelastic layer in the TB region. If drug is given as an aerosolized powder then the drug first needs to dissolve in the mucus layer. Although mucus as a very high water content, varying between approximately 90-95%, its viscosity may result in slow dissolution of drugs. Thus dissolution may be a rate determining step, especially for poorly soluble drugs, such as some of determining step, especially for poorly soluble drugs, such as some of the corticosteroids which are delivered as dry powder aerosols. Using mucolytic drugs such as N-acetylcysteine, which act to reduce mucus viscosity. Highly water soluble drugs, given as dry powder

aerosols, may dissolve at the very high relative humidity (>99%) present in airways air and impact as solution droplets. Once in solution, the drug will diffuse through the mucus layer and enter the aqueous environment of the epithelial lining fluid.

Current technology used for pulmonary delivery

Dry powder inhaler (DPI) have been most commonly used in these days to deliver the drugs via pulmonary route.

Dry powder inhalers (DPIs)

The drug is delivered to the airways as a dry powder aerosol. All currently available DPIs are breath-actuated, the respirable cloud is produced in response to the patient's effort.DPIs have the seceral advantages that includes.

- They do not require a propellant-which has undoubtedly been the driving force behind the introduction of a large number of novel devices in recent years.
- They eliminate the need for patient coordination of actuation and inhalation associated with pMIDs (Metered Dose Inhalers).
- The particles are travelling at a slower rate, thus excessive drug loss due to impaction in the throat is avoided.

  Every successful DPI requires development on two integrated fronts: powder technology and device design.

Powder technology

In addition to the drug powder, other powder excipients may be necessary. Successful delivery of the drug particles into the lungs requires that particle size should be controlled to <5 µm MMAD. Conventionally, this has been achieved by micronization, although more recently spray-drying and supercritical fluid technologies have been employed. However, particles of such small sizes exhibit exceptionally high surface energies, so that.

- Particle aggregation readily occurs, making redispesion a difficult process;
- The formulation has poor flow and entrainment properties.

The most frequently employed approach to overcoming the problems associated with particle size is to use a carrier particle such as lactose. When the micronized drug is blended with a carrier of much larger size range (usually 20-100µm) many of the drug particles become loosely associated with the lactose surface. When air forced through such a powder bed by the patients inhaling, the bed dilates. The turbulent airflow within the device detaches the drug particles from the carrier particles within the device itself; the drug particles are then carried on the airstream into the lungs. Those carrier particles that escape from the device are largely deposited in the oropharynx of the patient.Although high levels of turbulence will facilitate stripping of the drug particles from the carrier particles within the device, this course of action will also lead to an increase in resistance of the inhaler to airflow and thus to difficulties in inhaling through the device at a flow rate which produces optimum drug delivery. One way to provide high levels of turbulence without imposing large increases in airflow resistance is the judicious use and placement of grids of varying mesh sizes it is observation such as these which emphasize the need for parallel development of device design and powder technology. More recently ternary powder blends have been claimed to provide a higher fine particle fraction of the drug when subjected to an aerosolization process.

Future technology for pulmonary targeting

New technologies are also addressing the pulmonary delivery of the "new biotherapeutice", the products of biotechnology and molecular biology such as peptides, proteins and gene therapies which have been descried. Biopharmaceuticals under investigation for potential pulmonary delivery include those for local and systematic effect. Much effort is also currently being expended on the development of novel drug delivery system for pulmonary drug delivery, it possible to control:

- The duration of local drug activity , or
- The plasma level of systematically active agents

  A number of novel drug delivery system have been identified as potential system for controlling drug-release with in lung and include:
  - Liposomes
  - Bio erodible microsphere composed of polymers such as polyesters (e.g. poly lactic-co-glycolic acid) and polyanhydrides or naturally derived macro molecules such as albumin; Drug-carrier conjugates, e.g. drug-cyclodextrin inclusion complexes and covalently linked drug-dextran.

Tracheobronchial deposition of such carriers may not be desirable as clearance on the mucocililary escalator will occur in a relatively short time providing insufficient time for release from these controlled release system. Alveolar deposition will, in contrast, result in extended clearance time which are depended on the nature of the carrier a particle and may therefore be a better option the effective use of such carrier system for pulmonary drug delivery.The rate of liposome accumulation alveolar type-II cells is dependent on lipid composition. It is therefore possible to select liposome compositions displaying minimal interaction with these cells and thereby functions as controlled-release system for entrapped solutes. Delivery of novel colloids to the lung has largely focused on nebulization procedures, primarily because DPIs and pMDIs are typically incapable of depositing a large percentage of the emitted dose in the peripheral lung. For liposomes, size and compositions are important in maintain liposome integrity and hence entrapped drug during the nebulization process. There is some evidence to suggest that liposomes, as well as microspheres, may be administered in powder form utilizing DPIs.[1]

Novel drug delivery systems have emerged embracing various routes of administration, to attain targeted and controlled drug delivery. Drug encapsulation in the vesicles is one such system which helps to prolong drug duration in systemic circulation and decreases the toxicity by selective uptake. Based on this technique, a number of vesicular drug delivery systems such as liposomes, niosomes and provesicular systems like proliposomes and proniosomes have been developed**.**To resolve this stability issues, proliposome approach has provided a major breakthrough by using dry, free-flowing product, which is more stable during sterilization and storage.[2]

Colloidal particulate carriers such as liposomes or niosomes have been widely employed in drug delivery systems and producing them from proniosomes provides them a distinctive advantage. These carriers can act as drug reservoirs and the rate of drug release can be controlled by modification of their composition. Due of their capability to carry a variety of drugs.[3]

These Proniosomes are liquid crystalline compact niosome hybrids which upon hydration form niosomes. They help in reducing physical stability problems involved with niosomes such as leaking, fusion, aggregation and provide convenience in dosing, distribution, transportation and storage showing improved results than conventional niosomes.[4]

Vesicles have been extensively used in various drug delivery systems like drug targeting controlled release and permeation enhancement of drugs, but, there remains certain draw backs to be addressed and can be avoided if they are prepared in dry form. Proniosomes, prepared in dry form and hydrated by agitation in hot water to form niosomes provide an alternative with prospective for drug delivery via the intranasal route.[5]

Improving drug delivery to the pulmonary system has been an area of increasing interest among several disciplines. Particulate carriers such as liposomes or niosomes have many attractive features as pulmonary drug delivery systems, particularly with respect to controlled delivery. One of the difficulties in practical application of these products has been the long-term stability of the niosomes. The stability problems of niosomes have been addressed.[6]

Niosomes

Niosomes formation from proniosomes by hydration. The niosomes can be prepared by hydration of proniosomes, where aqueous phase containing the drug should be added to the proniosomes with brief agitation at a temperature greater than the mean transition phase temperature of the surfactant**.**

Niosomes are non-ionic surfactant vesicles that are capable to entrap hydrophilic as well as lipophilic drug candidates because they have an infrastructure consisting of both hydrophilic and hydrophobic moieties together. Niosomes are also somatically active, stable, providing the stability of entrapped drug. They are advantageous than other vesicles as being cheap and chemical stability. All methods traditionally used for preparation of niosomes are time consuming and many of them need specialized equipment's. Most of these methods allow only for a predetermined lot size, so material is often wasted if smaller quantities are required for particular dose application. The size of niosomes is microscopic and lies in Nano metric scale.

The particle size ranges from 10-100 nm.[7, 8]

Formation of Niosomes from Proniosomes

The niosomes can be prepared from the proniosomes by adding the aqueous phase with the drug to the proniosomes with brief agitation at a temperature greater than the mean transition phase temperature of the surfactant (Fig 1).

$T > Tm$

Where,

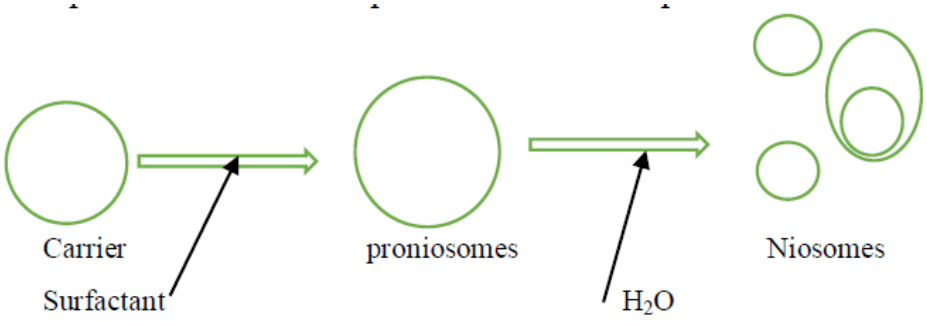

Fig 1: Formation of Niosomes from Proniosomes.

Blazek-Walsh A.I. et al has reported the formulation of niosomes from maltodextrin based proniosomes. This provides rapid reconstitution of niosomes with minimal residual carrier. Slurry of maltodextrin and surfactant was dried to form a free flowing powder, which could be rehydrated by addition of warm water.[3]

Niosomes are widely studied as an alternative to liposomes. These vesicular delivery systems have attracted considerable attention in topical/transdermal drug delivery for many reasons. Their effectiveness is strongly dependent on their physiological properties, such as composition, size, charge, lamellarity and application conditions.

Disadvantages of Niosomes

1. Physical instability
2. Aggregation and Fusion
3. Leaking of entrapped drug
4. Hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion.[9]

Proniosomes

Proniosomes are dry formulations of surfactant-coated carrier, which can be measured out as needed and rehydrated by brief agitation in hot water. These "proniosomes" minimize problems of niosomes physical stability such as aggregation, fusion and leaking and provided additional convenience in transportation, distribution, storage and dosing.[10]

Proniosome-derived niosomes are superior to conventional niosomes in convenience of storage, transport and dosing. Stability of dry proniosomes is expected to be more stable than a pre-manufactured niosomal formulation. In release studies proniosomes appear to be equivalent to conventional niosomes. Size distributions of Proniosome-derived niosomes are somewhat better than those of conventional niosomes so the release performance in more critical cases turns out to be superior. Proniosomes are dry powder, which makes further processing and packaging possible. The powder form provides optimal flexibility, unit dosing, in which the Proniosome powder could be beneficial (Table No II).[11]

Advantages of proniosomes include

1. Avoiding problem of physical stability like aggregation, fusion, leaking.
2. Proniosomes are water soluble carrier particles that are coated with surfactant and can be hydrated to form niosomal dispersion immediately before use on brief agitation with hot aqueous medium. This has additional convenience of the transportation, distribution; storage and designing would be dry niosomes a promising industrial product.
3. Biodegradable, biocompatible and non-immunogenic to the body.
4. Shows controlled and sustained release of drugs due to depot formation.
5. Furthermore, unacceptable solvents are avoided in proniosomal formulations. The systems may be directly formulated into transdermal patches and doesn't require the dispersion of vesicles into polymeric matrix.
6. The storage makes Proniosomes a versatile delivery system with potential for use with a wide range of active compounds.[12]

Types of proniosomes

1. Dry granular type of proniosomes

Dry granular proniosomes are involves the coating of water-soluble carrier such as sorbitol and maltodextrin with surfactant. The result of coating process is a dry formulation in which each water-soluble particle is covered with thin film of surfactant. It is essential to prepare vesicles at a temperature above the transition temperature of the non-ionic surfactant being used in the formulation.

These are further categorized as follows

(a) Sorbitol based proniosomes

Sorbitol based proniosomes is a dry formulation that involves sorbitol as the carrier, which is further coated with non-ionic surfactant and is used as niosomes within minutes by addition of hot water followed by agitation. They are normally made by spraying surfactant mixture prepared in organic solvent onto the sorbitol powder and then evaporating the solvent. Since the sorbitol carrier is soluble in organic solvent, the process is required to be repeated till the desired surfactant coating has been achieved. The surfactant coating on the carrier is very thin and hydration of this coating allows multilamellar vesicles to form as the carrier dissolves.[13]

(b) Maltodextrin based proniosomes

The principal advantage with this formulation was the amount of carrier required to support the surfactant could be easily adjusted and proniosomes with very high mass ratios of surfactant to carrier could be prepared.[14]

1. Liquid crystalline proniosomes

When the surfactant molecule are kept in contact with water, there are three ways through which lipophillic chains of surfactant can be transformed into a disordered, liquid state called lyotropic liquid crystalline state.

These three ways are

- Increasing temperature at Kraft point (Tc).
- Addition of solvent which dissolve lipids.
- Use of both temperature and solvent.

Table No:II-Components used for the preparation of proniosomes.

Surfactants	Surfactant molecule contains both a water insoluble (lipophillic) and a water soluble (hydrophilic) component. Ex:- alkyl ethers, alkyl esters, alkyl amides and esters of fatty acids.[15]
Non-ionicAmphiphiles	1.Alkyl ethers and alkyl glyceryl ethers Polyoxyethylene 4 lauryl ether (Brij30), Polyoxyethylenestearyl ethers (Brij 72,76) PolyoxyethyleneCetylethers (Brij 52, 56, 58) 2. Sorbitan fatty acid Esters Span 20, 40, 60, 80 3. Polyoxyethylene fatty acid esters Tween 20, 40, 60, 80
Carrier materials	Maltodextrin, Mannitol, Sorbitol , Spray dried lactose, Lactose monohydrate Sucrose stearate, Glucose monohydrate
Membrane stabilizer	Carriers such as Cholesterol and lecithin components are mainly used as membrane stabilize.[16]
Solvent and Aqueous phase	Vesicles formed from different alcohols are of different size and they follow the Order: Ethanol > Propanol >Butanol> Isopropanol. Ethanol has greater solubility in water hence leads to formation of highest size of vesicles instead of Isopropanol which forms smallest size of vesicle due to branched chain present. Phosphate buffer: pH 7.4, 0.1% glycerol, hot water is used as aqueous phase in preparation or formulation of proniosomes.[17]

PULMONARY DRUG DELIVERY SYSTEM

Pulmonary drug delivery systems have been used for decades to deliver drugs for treatment of respiratory disorders. The lungs provide a huge surface area of alveoli with rich capillary network which acts as an excellent absorbing surface for administration of drugs. Throughout the past several years, rapid onset of action and higher efficiency has been responsible for the success of pulmonary delivery system for symptomatic relief in treatment of asthma and chronic obstructive pulmonary disease (COPD).[18]

Owing to the unique physiological features of the lungs, the pulmonary administration serves as an alternative route for systemic drug delivery.

These unique physiological features involve:

- The large and highly vascularized alveolar surface area for drug absorption
- Non-invasive systemic drug delivery
- Epithelial barrier of low thickness hence high solute permeability
- Less proteolytic activity
- By pass first-pass hepatic metabolism
- Rapid onset of action
- Through this route, drugs could be targeted to the airways of specific size or infected with a particular injury or disease within the lungs as opposed to other normal organs.

For example, ultrafine therapeutic particles have been introduced recently which causes drug deposition in deeper airways. Through this route, it is possible to deliver drugs to specific cells such as macrophages, lymphocytes, neutrophils, endothelial cells, or epithelial cells as well as organelles within a cell. The nature of the material will also affect the fate of drug uptake.[19]

ADVANTAGES

1. The ability to nebulize viscous drug formulations for pulmonary delivery, thereby overcoming drug solubility issues with the ability to use lipid, water or lipid/water emulsions as drug carriers.
2. Ability to nebulize viscous liquids into droplets in the 2-5μm range regardless of the carrier composition solubility which would allow for a wide range of drug formulation options.
3. Increased drug delivery efficacy due to size-stable aerosol droplets with reduced hygroscopic growth and evaporative shrinkage.
4. Niosomal drug formulations remain stable when nebulized.
5. Ability to nebulize protein-containing solutions.
6. For hand held inhaler applications, drug does not need to be emulsified in liquefied nebulizing gas to achieve aerosolization.

APPLICATIONS

Effective pulmonary delivery of any drug, be it water or lipid soluble, for the treatment of pulmonary disorders or for a systemic delivery.

LIMITATIONS

Limitations of pulmonary drug delivery systems including:

- stability of drug in vivo;
- transport;
- targeting specificity;
- drug irritation and toxicity;
- immunogenicity of proteins; and
- drug retention and clearance.[20]

Table No: III Recent research reported proniosome as drug delivery

SL No	Drug	Method of Preparation	Exipients	Reported
1.	Felodipine	Slurry method	Span60 and cholesterol	Felodipine loaded proniosomal formulations were successfully prepared. The percent drug release was found to be higher for formulation than pure drug.[21]
2	Piroxicam	proniosomes were prepared by coacervation phase separation method	Span 20, 40, 60 and 80, cholesterol, lecithin, Carbopol	Piroxicam was successfully entrapped within the lipid bilayers of the vesicles with high efficiency. The vesicles fuse with the intercellular lipid of the stratum corneum and transfer the drug from vesicles to the skin or there might be penetration enhancement due to surfactants.[22]
3	Granisetron hydrochloride	coacervation and phase separation method	span 60, cholesterol, soya lecithin	Formulation was optimized by use of 3x2 factorial design, Finally it will concluded that GRA HCl can be successfully formulated in proniosomal TDDS.[23]
4.	Ramipril	Proniosome powders were prepared by using slurry method	Span60, cholesterol	This approach can be used to improve the efficacy of the drug as well as to alleviate the adverse effects of the drug. The ramipril can greatly be advanced and improved using the provesicular approach.[24]
5.	Meloxicom	Proniosomes were prepared by the slurry method	Span60, Mannitol, cholesterol	The maltodextrin is a good carrier compared to mannitol. Percentage cumulative drug release was higher in maltodextrin as compared to mannitol while entrapment efficiency was less in Mannitol as compared to maltodextrin.. So the maltodextrin is a good carrier compared to mannitol.[25]
6.	Nebivolol	Proniosomes were prepared by using slurry method.	Span60, cholesterol Span40, Lecithin	Proniosomes gave satisfactory results for entrapment efficiency. In-vitro drug release behavior was improved. There is no significant difference between the FTIR patterns of the optimized formulation of proniosomal powder and to that of the pure drug.[26]
7.	Permethrin	Proniosomes were prepared by using modified slurry method	Cholesterol, Brij97 Aerosil200	Permethrin 5% micro emulsion-based hydrogel proved to be homogenous, stable, and clinically effective, compared with the topical powder that was unstable under accelerated stability conditions.[27]
8.	Cephalosporins	Proniosomes were prepared by using slurry method.	Span60, cholesterol, Maltodextrin	It will lead to sustained action of the entrapped drug that reduce the side effects associated with frequent administration of the drug and potentiate the therapeutic effects of the drug.[28]
9.	Risperidone	Risperidoneproniosomes were prepared by Coacervation phase separation method	Span 20,40,60,80 and tweens 20,40,80, cholesterol, stearylamine and soya lecithin	The designed transdermal system could be a better alternative in risperidone therapy in the management of various neuro-psychiatry disorders.[29]
10.	Domperidone	Proniosomal gel can be prepared by the use of coaservation phase separation method	Span20,40,60,80 ,Maltodextrin, Sobitol, Mannitol, Cholesterol and lecithin	Domperidone successfully entrapped within the lipid bilayers of the vesicles with high efficiency. Proniosomes will be a promising carrier for Domperidone and other drugs, especially due to their simple production.[30]

11.	Valsartan	Valsartan proniosomes were prepared by coacervation phase separation method.	Span40, Span 60 Soya lecithin (95%)	These proniosomes were also found to be quite stable at 4-8^{o}C over a one-month period. This work has established the foundation for future study on the potential of valsartan-loaded niosomes for a transdermal delivery system.[31]
12.	Hydralazine HCL	Proniosomal gel was prepared by phase separation coacervation technique.	Soya lecithin, Span 20,40,60	Proniosomal gel will be suitable drug delivery system for Hydralazine HCl due to ease of preparation and incorporation of less number of excipients.[32]
13.	Norfloxacin	Slurry method	Maltodextrin,span60,cholesterol	proniosomes using maltodextrin as a carrier is a promising approach to sustain the drug release from an extended period of time and thus reducing the side effects related to GI irritation.[33]
14.	Carvedilol	Proniosomal gel was prepared by phase separation coacervation technique.	Span20,40,60, Tween20,80 Cholesterol, lecithin.	proniosomal gel formulations were evaluated for the encapsulation efficiency, vesicle size and shape. the results were found in the acceptable range.[34]
15.	Curcumin	Ether injection method.	Span80,cholesterol	These proniosomal formulations should be kept refrigerated to achieve best stability. However, in-vivo studies are required to prove their actual utility as vehicles for transdermal drug delivery.[35]
16.	Tretinoin (TRT)	Preparation of proniosomes by slurry method	Span40,60 D-Sorbitol Cholesterol9% and Tween 20 Carbopol	The encapsulation of TRT in proniosomes provided the overcoming solubility and skin irritancy problems. Finally this study emphasize the potential of TRT-loaded proniosomes as a topical drug delivery system for enhancing the acne treatment efficacy of TRT while reducing its side effects.[36]
17.	Sumatriptan succinate	Proniosomes were prepared using Co-acervation phase separation method	Span20,40,60, 80 lecithin, and cholesterol	Sumatriptan succinate can be formulated as proniosomes for transdermal delivery to improve bioavailability by passing the first pass effect.[37]
18.	Ibuprofen	Proniosomal gel was prepared by phase separation coacervation technique.	Span 20,80 and soya lecithin cholesterol.	Promising drug delivery system for BCS (Biopharmaceutical Classification System) class II drugs such as ibuprofen and especially this method is easy to prepare, economic and reproducible. proniosomal gel drug delivery approach for various therapeutic drug candidates with commercial viability.[38]
19.	Capecitabine	Proniosomal gel was prepared by phase separation coacervation technique.	Span80,60 tween60,80 Soya lecithin Cholesterol.	proniosomes are a very promising carrier for the topical administration due to the enhanced delivery of drugs through the skin thus prompting various opportunities for the development of suitable therapeutic strategies through the topical route.[39]
20.	Tolterodine Tartrate(TT)	Proniosomal gels were prepared by coacervation phase separation method	Span, cholesterol , Lecithin	TT formulations can have efficacies comparable with those of oral formulations for OAB(overactive bladder) and, also, cause less dry mouth effects. These results can serve as a foundation for future studies on the potential of proniosomal gels for transdermal TT delivery.[40]
21.	Ritonavir	Proniosomes were prepared by coacervation phase separation method	Span20,40,60,80, tween20,40,60,80 carbopol-934	Ritonavir proniosomes sustained the release of drug over 12 hrs. Delivering it transdermally and helped to reducesd side

			Cholesterol Lecithin	effect associated with other system. Thus proniosomal gel system shown potential for delivery of suitable drug candidate Ritonavir.[41]

REVIEW OF LITERATURE

- **Moazeni*et al*(2010).,** developed a noisome-encapsulated Ciprofloxacin HCl formulation for pulmonary delivery and studied the feasibility of encapsulation of Ciprofloxacin HCl in noisome, its stability and nebulization capability. They reported that the formulations composed of Span 60 and Tween 60 in combination with 40 mol% of cholesterol exhibited high encapsulation efficacy and stability and also had fine particle fraction and nebulization efficiency of about 61.9% ± 1.0 and 77.9% ± 2.8, respectively.[42]
- **Sweeney LG *et al*(2005).,** Utilized spray-freeze drying method to manufacture a liposomal powder formulation containing Ciprofloxacin. They assessed the aerosol properties of this formulation using a new passive inhaler, in which the powder was entrained at a flow rate of 60 l/min. Their results concluded that reconstitution of the powder in various aqueous media changes the drug encapsulation efficiencies.[43]
- **Berkland C *et al*(2009).,** stated that nanoparticle technology represents an attractive approach for formulating poorly water-soluble pulmonary medicines. Unfortunately, nanoparticle suspensions used in nebulizers or metered dose inhalers often suffer from physical instability in the form of uncontrolled agglomeration or Ostwald ripening. Their results suggested that the dissolution rates of dried nanoparticle agglomerate formulations were significantly faster than that of stock Budesonide and also that nanoparticle agglomerates possess the microstructure desired for lung deposition and the nanostructure to facilitate rapid dissolution of poorly water-soluble drugs.[44]
- **Elhissi A *et al(*2010).,** have developed liposomes loaded with Salbutamol sulphat and Beclometasonedipropionate included with in separate and same formulation. Their study demonstrated the possibility of producing stable freeze-dried liposomes that included two anti-asthma drugs and also demonstrated a potential for application in pulmonary delivery.[45]
- **Emami J *et al*(2015).,** Budesonide-loaded solid lipid nanoparticles were prepared by the emulsification-solvent diffusion method. Their results provided fundamental data for the application of SLNs in pulmonary delivery system of budesonide.[46]
- **Amani A *et al*(2016).,** have developed the lipid nanoparticles for pulmonary applications are possibility of deep lung deposition with prolonged release and low toxicity. There *in vitro* aerosolization performance of Budesonide - nanoparticles was compared to that of commercial budesonide which indicated enhancement in fine particle fraction value.[47]
- **Chono S *et al* (2006).,** incorporated Ciprofloxacin into liposomes for pulmonary administration. Their findings suggested that efficient delivery of Ciprofloxacin liposomes with a particle size of 1000 nm induces an excellent antibacterial effect without any cytotoxic effects on lung tissues. Therefore, Ciprofloxacin -liposomes may be useful in the development of drug delivery systems for the treatment of respiratory infections caused by intracellular parasites, such as Mycobacterium tuberculosis, Chlamydia pneumonia and Listeria monocytogenes.[48]
- **Suzuki H *et al*(2011).,** developed PEGylated liposomes of Ciprofloxacin for the treatment of respiratory infections. According to pharmacokinetic/pharmacodynamic analysis, the PEGylated Ciprofloxacin -liposomes exhibited potent antibacterial effects against pathogenic microorganisms. This study showed that PEGylated Ciprofloxacin -liposomes were a useful aerosol-based pulmonary drug delivery system for the treatment of respiratory infections.[49]
- **Zhangy Y *et al*(2016).,** developed stable and well-dispersible budesonide Nano suspensions by micro fluidizer method. The data showed that BUD Nano suspensions have the most outstanding deposition distribution with fine particle ratio 82.2%.[50]
- **Yang JZ *et al*(2008).,** studied pharmacokinetic behavior of Fluticasone and Budesonide Nano suspensions in pulmonary delivery. The pharmacokinetic studies after the intratracheal administration of Nano suspensions showed deep lung deposition and fast lung absorption, with solubility playing an important role in lung retention and duration of action.[51]

CONCLUSION

Pulmonary drug delivery is a widely used route for locally acting drugs in recent days. The future research will be focused on the production of inhalation on the market which contain systemically acting drugs.From the above review it is concluded that the concept of encapsulated the drug into proniosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians. Proniosomes derived niosomes represent a promising drug delivery module. They represent a structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes, due to the niosome ability to encapsulate different type of drugs within their multienvironmental structure. Proniosomes based niosomes are thoughts to be better candidates drug

delivery as compared to liposomes due to various factors like cost, stability etc.

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