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ADVANCEMENT IN BUCCAL DRUG DELIVERY FOR CONVENIENT ORAL INSULINADMINISTRATION

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ABSTRACT

The buccal mucosa drug delivery system refers to the administration of the drug through the buccal cavity as a site of drug absorption. Diabetes mellitus is one of the most lethal, non-communicable diseases. Insulin is normally used to medicate diabetes. Due to bioavailability issues, the most regular route of administration is through injection, which may pose compliance problems to treatment. The insulin gets absorbed directly into the bloodstream through the buccal mucosa, which is the inner liningof the cheek. Oral insulin spray is a novel drug delivery system that offers an alternative to the subcutaneous route of administration. The goal of this inventive approach is to improve patient compliance and convenience by abolishing the need for painful injections. Results showed that the oral insulin absorption and elimination was much faster when compared to subcutaneous injections and outperformed subcutaneous injections in terms of glucose and C-peptide lowering capacity as well asrise in the insulin levels.

KEYWORDS: Buccal drug delivery system, oral insulin spray, novel drug delivery system, bioavailability issues.

BUCCAL MUCOSA DRUG DELIVERY SYSTEM: ORAL INSULIN SPRAY

INTRODUCTION TO DRUG DELIVERY SYSTEM

A drug delivery system is a technology that carries drugs into or throughout the body. It improves its efficacy & safety by helping the medicines to reach the right spot at the right time. This procedure takes place by.

- Administrating the therapeutic product,
- Releasing of the API,
- The transport of the API to the site of action across the biological membranes.[1]

Characteristics

- It must provide controlled drug delivery.
- t should be easy for patients to administer.
- It must increase the bioavailability by making the drug more effective.
- It must ensure patient well-being by being safe and reliable.[2]

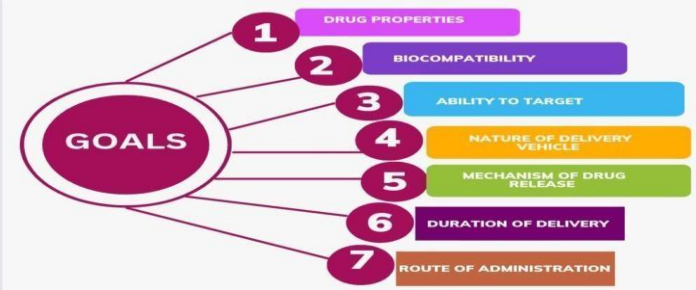

Figure 1: Goals of drug delivery system.

Various types of controlled drug delivery systems

1. Sustained release DDS [SR] Eg. Verapamil
2. Extended DDS [XR] Eg. Effexor
3. Modified DDS [MR] Eg. Cellulose acetate phthalate
4. Site Specific DDS [SS] Eg. Zidovudine
5. Delayed Released DDS [DS] Eg. Protonix
6. Prolonged Action [PR] Eg. Metformin
7. Immediate Released DDS [I] Eg. Narcotic drugs

The drug delivery system can further be split into two main types:

1. Conventional drug delivery system.
2. Novel drug delivery system.

1. **Conventional drug delivery systems:** This system includes tablets, capsules & ointments, etc.
2. **Novel drug delivery system:** This includes the mixtures of advanced techniques & new drug formwith controlled drug release to target at the specific site.[3]

BUCCAL DRUG DELIVERY SYSTEM

Introduction

The buccal drug delivery system includes administration of drugs through buccal mucosa to the systemic circulation (in the lining of the cheeks). This route of drug delivery offers a great lead over other routes of administration which includes.

- Bypassing the first pass effect and delivering the drug directly to the systemic circulation.
- To prevent presystemic removal in the GI tract.

These advantages make buccal drug delivery very achievable. The buccal mucosa consists of a rich blood supply. It is relatively permeable when compared to other routes of administration which includes rectal route, sublingual and nasal route, with lower patient compliance.[4,5]

Advantages of Buccal Drug Delivery System

- It works rapidly giving fast onset of action.
- Quick absorption due to good blood supply and blood flow.
- The drug is protected from degradation in the acidic environment of the GIT.
- Better patient consent.
- Less painful and less annoying.[6]

Demerits of Buccal Drug Delivery System

- Ulcerogenic property occurring due to long term exposure to the drug.
- Risk of choking by involuntarily swallowing.
- Swallowing saliva while using the buccal drug delivery system can result in the loss of the
- drug, reducing its effectiveness.
- It has smaller surface area.[7]

Permeability of drug via Buccal route

The two routes of drug absorption via buccal mucosa are.

- The transcellular route in which the drug passes through the cells.

- Paracellular route in which the drug passes between the cells.

These routes play a crucial role in drug permeability. (Nicolazza J.A. et al., 2005)[8]

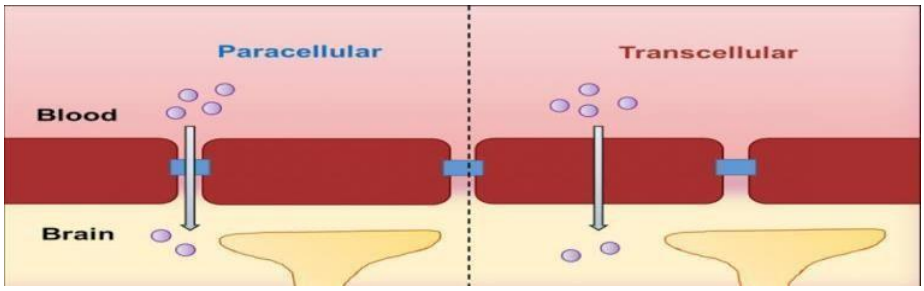

Figure 2: Buccal mucosa routes.

Factors affecting drug delivery via buccal route

Factors affecting drug delivery via buccal route are split into 3 main types.

1. Polymer related factors
2. Environment Related factors
3. Physiological variables.[9]

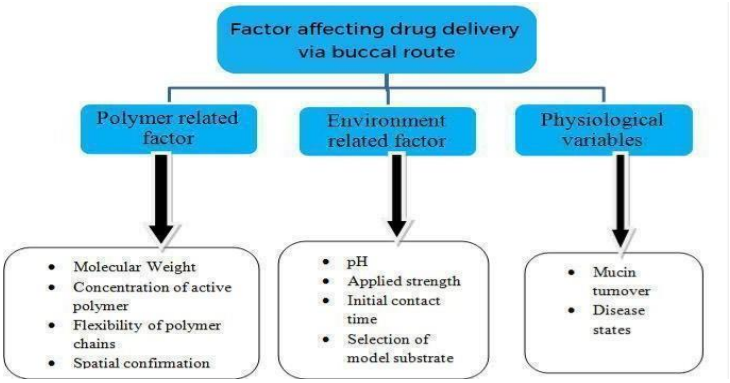

Figure 3: Factors affecting buccal drug delivery.

Introduction to insulin

- Insulin is a vital hormone which is produced in pancreas by β cells of islets of Langerhans.
- It helps to converts food into energy and control blood sugar levels.
- It maintains the normal blood glucose levels by promoting cellular glucose uptake
- balancing carbohydrate and protein and facilitating cell division and growth.[10]

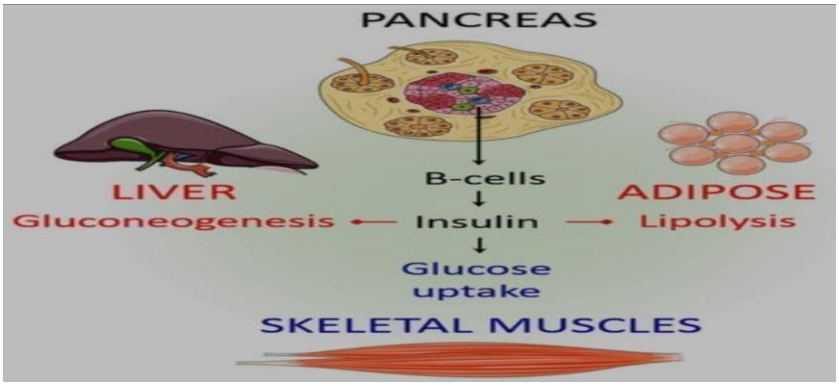

Figure 4: Insulin secretion.

- Insulin is made up of 51 amino acids which plays a major role in cell multiplication & metabolism.
- It is an important therapeutic which treats patients suffering from diabetes mellitus.
- Many individuals with diabetes need insulin to keep the blood glucose levels in check.
- Subcutaneous route is the most standard route of insulin delivery.

Figure 5: Approaches of insulin.

- The subcutaneous route of insulin administration is associated with needle pain, injectionphobia and less compliance.
- The other routes for administering insulin are oral, buccal, nasal, peritoneal and transdermal.(Ruegsegger, G.N and Cortes 2018)[11]
- Oral (B) Nasal (C) Pulmonary (D) Subcutaneous (E) Transdermal.

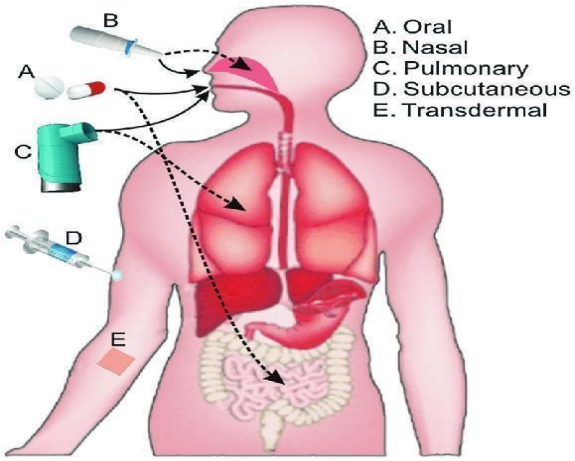

Figure 6: Routes of insulin administration.

History of insulin

In 1921, researchers from the university of Toronto, including Sir Fredericks G Banting introduced the discovery of insulin, which is used for treating diabetes. In 1978, David Goeddel discovered the first rDNA human insulin. He cleverly utilized and combined the insulin chains A & B in Escherichia coli.This improvement paved the way for more effective insulin production.[12]

January 2006 Pfizer bought the worldwide rights to *Exubera* first oral insulin spray from Sanofi- Aventis and withdrawn from market 2007. Afrezza an oral insulin spray by ManNkind corporation insulin is currently available in the United States for adults living with type 1 or type 2 diabetes via prescription from 2014. Brazil recently got approval 2019.

ORAL INSULIN SPRAY

Figure 7: Oral insulin spray.

INTRODUCTION

The delivery of insulin subcutaneously is a standard route for patients with diabetes, even if the patient's compliance due to injections is difficult to achieve. That is why alternative forms of deliveryare being tested, like oral administration.[13] Oral administration of insulin helps to reduce needle pain and the risk of skin infection. It also helps avoid side effects such as hyperinsulinemia, weight gain, and hypoglycemia. There's a new approach called oral insulin spray, which is a non-injectablepractice of insulin delivery. It delivers insulin as an aerosol of uniform-sized droplets at rapid speed into the oropharyngeal cavity for absorption through the mucous membranes. Oral routeis regarded as the most appropriate and suitable route of drug administration in case of chronic therapy. Oral insulin spray benefits in achieving patients compliance and attachment. In addition, withphysiological merits. Eliminating the need for multiple daily injections, it also helps overcome psychological barriers. Oral insulin is superior as it directly delivers to the primary site of action, theliver.[14]

Oral insulin spray analog (IN-105)

- IN-105 is a development in oral insulin.
- It's second-generation of insulin analog that has some attractive qualities.
- It is a human recombinant insulin which binds with polyethylene glycol through an acetylchain.
- Compared to insulin, IN-105 shows lower mitogenic potential while retaining similar pharmacological activity as insulin.
- IN-105 shows no issues in acute dose toxicity in preclinical studies
- Various investigations regarding mutagenicity, teratogenicity, genotoxicity shows nothing.
- IN-105 displays absorption and effectiveness by circulating insulin levels within 20 minutes,with a maximum drop in glucose levels around 40 minutes.
- It has demonstrated improved half-life in the GIT, lower immunogenicity and absorption incomparison with insulin.
- Its absorption is proportionate to the dose administered. (Agarwal V, Khan MA 2001)[15]

APPROACHES OF ORAL INSULIN SPRAY

Various approaches are applied to improve the bioavailability of oral insulin to protect the insulin from enzymatic destruction in the digestive tract and also boost the permeability of intestinal layer.[19]

Table 1: Approaches of oral insulin sprayMechanism of oral insulin spray.

Approach	Examples	Limitations
1.Absorption enhancers	Sodium glycolate. camostat mesilate and bacitracin	Protein malabsorption
2.Chemical modification for endogenous receptor-mediated absorption	Bile salts, non-ionic surfactants, sodium dodecyl sulphate andlysolecithin	Toxins and intestinal flora are accessible to the systemic circulation, acutedamage to the intestinal wall
3.Chemiccal modification for endogenous receptor-mediated absorption	Transferrin conjugation	Transferrin conjugation
4.Mucoadhesive polymers	chitosan and PLGA	Insulin is more susceptible to enzymatic degradation

Insulin for oral delivery

- Pass through oral cavity.
- Pass through intestinal lumen.
- Pass through the apical mucus layer.
- Pass through water layer.
- Ability to cross epithelial cells of intestine.
- Through the basement membrane.
- Ends up inside the blood vessel.[16]

Advantages of oral insulin spray

- It helps in reducing pain from injection.
- Reduces skin infections.
- Improves the portal levels of insulin.
- Most successful and acceptable route of delivery.
- Patient compliance.
- It is effective in reducing glucose instability.[17,18]

Disadvantage of oral insulin spray

- Low oral bioavailability.
- Poorly permeable across the intestinal epithelium.
- Insulin undergoes rapid degradation.
- Infusion site reactions.
- Cost of pump and supplies.[17,18]

DOSAGE OF ORAL INSULIN SPRAY MEDICATION

The dosage of buccal insulin spray which is a current invention can be delivered either in a single doseor can be split into multiple doses throughout the day. It can be administered three to four times a daywhich can be-before breakfast, lunch and supper. This oral spray of insulin is usually recommended tobe taken one hour prior to meal.[29]

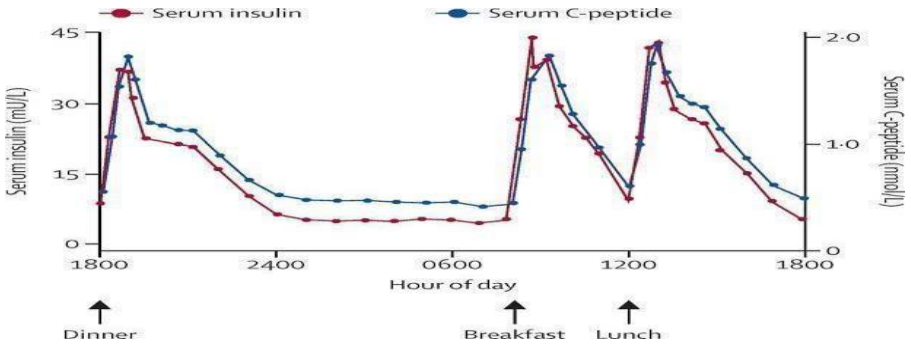

Figure 8: Graph of dosage of oral insulin spray.

The dosage of the insulin spray has no particular restrictions.

- It must be administered according to the conventional doses.
- The specific dosages may vary depending on the factor like bioavailability, individual'spatients & seriousness of the conditions.
- Hence it should best be consult will a physician.
- The buccal insulin spray is designed to have a huge contact area with the buccal mucosa whichallows safety, quick absorption and a great hypoglycaemic action.
- The formulation of insulin spray comes in a bottle with a constant delivery pump, spraying themist of the drug formulation into the buccal cavity.
- The insulin gets sticks to the buccal cavity & get absorbed quickly via mucosa into the systemiccirculation. Thus, it reaches the body quickly & efficiently.
- One of the great benefits of the buccal spray is that it helps to improve the rate of absorption.
- In addition, the acidolysis that occurs in a digestive tract& the first pass liver effect can be prevented.
- Overall, the insulin buccal spray offers a convenient & effective non-injectable choice forinsulin administration.
- It is designed to be patient-friendly. (Schilling RJ and Mitra AK 1999)[20]

Oral insulin spray: Formulation

The current discovery of buccal spray consists of insulin which is absorbed rapidly in the bloodstreamthrough buccal mucosa route.

- The efficiency and stability of oral insulin spray is significantly improved.
- This administration is convenient.
- It consists of diameter less than 200 nm.[21]
- It is a microemulsion which comprises 1000µ-7000µ.
- The oral insulin spray consists of

➢ Human recombinant insulin (Humulin R)
➢ Surfactants
➢ Solubilizers
➢ Micellating agent
➢ Emulsifying agent

Formulation of insulin spray

Example

1. Soybean lecithin (absorption promotes): 5- 50g
2. Propylene glycol (cosolvent) : 20-80g
3. Phosphate buffer (pH) : 6-7.8 pH

Preparation Method

A. Absorption promoters is added to co-solvent. After mixing, a phosphate buffer is added to theresulting solution and solicited oil phase. Thus, microemulsion is obtained.
B. Insulin is dissolved in a phosphate buffer.
C. Insulin solution is added to the oil phase and sonicated again to agitate particles.
D. Thus, insulin emulsion is obtained.
E. The resulting solution is the mixture of stabilizer and absorption enhancers.
F. An aerosol consisting of uniform-sized particles is attained.[22]

Polymers of oral insulin spray

- Natural polymers helpassist in delivering insulin orally.
- Natural polymers used in oral insulin spray-

A. Chitosan. Weak polysaccharides
B. Alginate

C. Dextran
D. Pectin
E. Starch
F. Cyclodextrin
G. Tragacanth

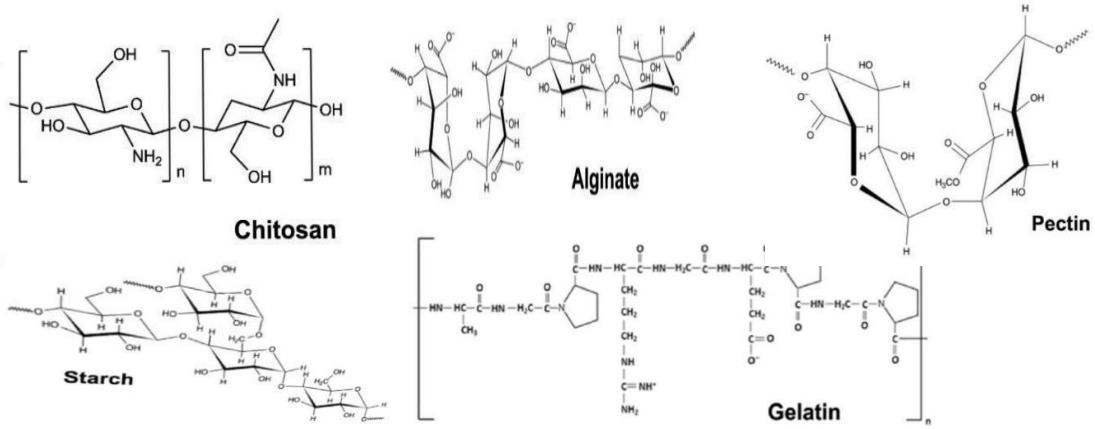

Fig 9: Natural polymers.

Properties of natural polymers

Polymers	**Sources.**
Chitosan	Crustaceans.
Alginate.	Algal.

SPECIFICATIONS OF CARRIERS

- Carrier used in oral insulin should have better resistance against enzymes change of pH.
- It should produce a compatible and steady environment to show that insulin is naturally act.
- It should avoid the degradation caused by enzymes.
- The permeability of insulin should be enhanced inside the intestinal membrane.
- The intestinal residence time should be extended.
- It should not be harmful after oral administration.
- It should deliver the insulin fast enough and in a precise quantity to control glucose concentration in blood.[22,23]

METERED DOSE INHALERS: (MDI)

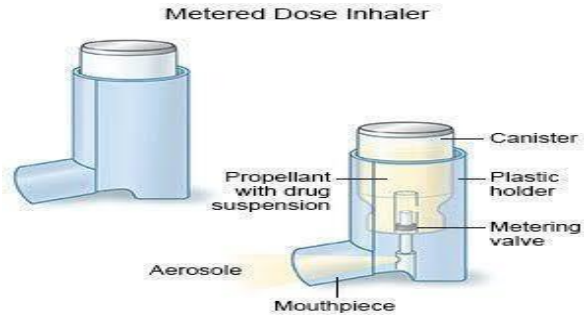

Figure 10: Metered dose inhaler.

Oral-lyn, a brand-new liquid aerosol formulation created by Generex Biotechnology, is now undergoing phase ii clinical trials. Through the use of a metered dose inhaler, Oral-lyn delivers accurate insulin doses as tiny, aerosolized droplets that are directed into the mouth.

- Oral-lyn consists of a mixed micellar solution which contains insulin & absorption enhancers.
- Every single puff administers 10U insulin dosage carrying an absorption rate of 10% which leads to 1U of insulin getting absorbed.
- Clinical trials involving patients with type 1& type 2 diabetes & healthy individuals found that Oral-lyn exhibits an absorption profile which is dose dependent, which shows a quicker onsetand a limited duration compare to insulin injected subcutaneously.[24]

COMPONENTS OF METERED DOSE

- The components of metered dose include the propellant formulation, metering valve & actuator.
- The drug is delivered to the specific site through these components of metered dose
- Each part of the MDI is crucial for the successful working of this device.[25]

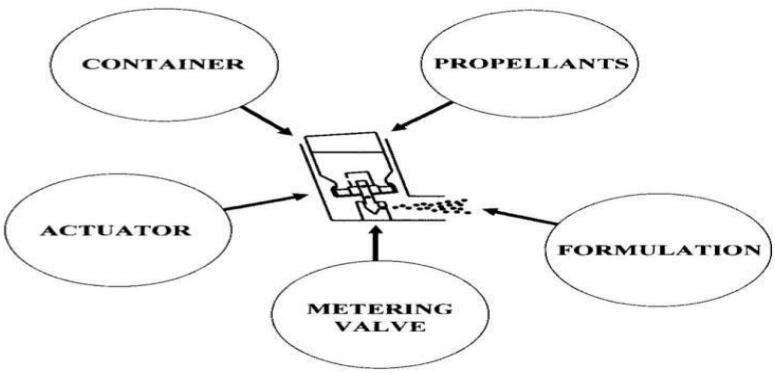

Figure 11: Components of pMDI.

1. **Container / Canister**

Container used for MDI should resists the excessive pressure produced through propellants. Inert materials such as stainless steel, aluminium, glass etc must be used to build the container.

- Aluminium is preferred over glass as it is light, less fragile & more compact. It should be lightin weight.
- It should be oxygen proof, water proof. The device holds the drug inside.

2. **Formulation of drugs**

- The drug used in the MDI are in the form of solutions or suspensions.
- 2 micronation methods carried out on jet mill is required to prepare suspensions.
- Suspensions are mostly used in MDI.
- If a suspension is delivered through MDI, then surfactants (such as oleic acid, sorbitan trioleate)are added to reduce particle aggregation.
- If a solution is delivered through MDI, then the suitable co-solvents must be used in the drugformulation.
- The excipients are used to increase the solubility of drug in propellant.
- Hence a particle size of 1.0-1.5 mg of the dose per shot is obtained.

3. **Propellant**

- Propellants are defined as the pressurized liquefied gases present in a gas state at air pressureand when compressed forms liquid.
- The propellants used should be
- Non-toxic
- Non-flammable
- Suitable with the formulated drugs.
- Should have a suitable boiling point.

Chlorofluorocarbons (CFCs) have been used as the propellants.

- CFC-12 (dichlorodifluoromethane) which is highly volatile was being used as the majorcomponent.
- It is added at low temperature into the container before the meter valve is crimped or throughthe metering value after crimping.
- Inside the container, the CFC forms 2 phase system the liquid and Saturated vapour

- The phase is formed such that the dynamic equilibrium exists between liquid & vapour phase.
- The use of CFC was later banned
- 2 hydrofluoroalkane (HFA-134a&227) formulation are currently showing up in the market.
- These HFAs have the thermal characteristics as chlorofluorocarbon-12.Dimethyl ether, propane, butane can also be looked at as propellant but propane & butane are likely to be rejected as they are flammable.

4) Metering Valve

- Metering valve is an essential part of MD
- It is crimped onto the container.
- It consists of the volume ranging between 25-100 uL
- Various designs of metering valve are available.
- Before the discharge, the channel is opened between the container body and the meteringchamber.
- After the discharge, the channel between the container body and metering chamber closes whilethe channel between metering chamber and the air opens.
- The compressed drug preparation is discharge out to the valve stem. This along with theactuator forms an expansion reservoir.
- Canister used should be in an inverted position such that the valve lies beneath the container.

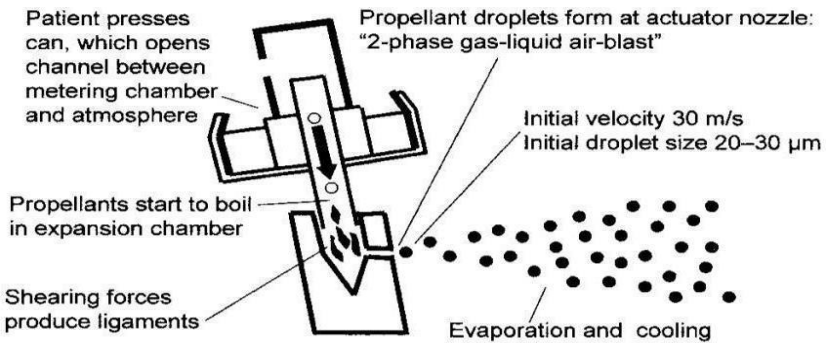

Figure 12: Formation of pMDI.

- Valve is faced below the container so that it gets refilled under gravity.
- Few valves contain the retaining cups which carries the next doses of drug.

5. **Actuator**

- The container is placed inside the actuator which is used by patients.
- Aerosol particle size ranges between 0.14-0.6 mm.
- This is determined by the nozzle diameter.
- The particle size can also be altered by changing the nozzle pathlength of the actuator.
- The actuator spray tip is essential for the formation of spray.
- The last spray formation process is depicted as two- phase gas or fluids air burst.
- As the dose exit the sprayer, the particles attached to propellant vapours are separated by airresistance.
- This forms a scattering of the fluid particles.
- Vaporization of the propellant cools the droplets
- This causes the spray to feel cool inside the buccal region.[26]

Advantages of metered dose

1. MDI is small and portable
2. They are quick and convenient to use
3. MDIs are usually inexpensive.
4. More than 100 doses are available.
5. MDIs can be easily handled.
6. It protects the drug formulation from light and oxidation
7. It can deliver the spray uniformly and the volume of liquid doses is delivered accurately.
8. The cost of unit doses is low.
9. It protects against bacteria and moisture.
10. They are unobtrusive.[26,27]

Disadvantages of metered dose

1. It requires the use of propellants which is harmful to nature.
2. The delivery of drug depends on good inhaler technique and hand-mouth coordination.
3. Not suitable for paediatrics.
4. It is difficult to deliver high doses.
5. It cannot be used for proteins and peptides as there might be chances of getting denaturedwhen it comes in contact with propellants
6. The size of the dose being administered is limited.[27]

DIFFERENCE BETWEEN DPI AND MDI

Table 2: Difference between DPI & MDI.

Dry powder inhalers	Metered Dose inhalers
It delivers the dry powder aerosol.	It delivers mist of drug particles
Solid particles are present	Solution or suspensions are present.
The drug is in micronized from alone or with a carrier	The drug is mixed with propellants
Single or no excipients are used	The dose can be measured
The drug is delivered in the form of particles in capsules	The drug is delivered in the form of liquid mixtures

CURRENT STATUS

- Generex Biotechnology created a liquid composition of recombinant human insulinwhich is in the form of a spray
- By using rapid mist devices, this liquid form of human insulin is sprayed.

➢ Insulin is absorbed through the mucosa of buccal cavity

➢ The dosage form is delivered as a fine spray mist to the buccal cavity.

➢ Oral-lyn provides an effective substitute to prandial subcutaneous injections ofinsulin. It also improves patient consent with insulin therapy.

➢ It is planned in a split dose manner which implies that patient must consume half of the dose right before a meal & the other half immediately after the meal.

➢ So far, Oral-lyn has been approved in several countries including Ecuador, India, Lebanon, Algeria, US & Canada.

➢ It has also be tested in 30 different clinical trials demanding a vast number ofsubjects.[28]

MARKETED PRODUCTS

Table 3: Marketed product*

Oral-Lyn is a spray formulation of human insulin indicated for thetreatment of type and 2 diabetes
Drug (brand / generic) Oral-lyn
Therapy class Insulins
Company/ Licence Generex Biotechnology
Product description Oral spray formulation of human insulin.

- Clinical studies of the medication Oral-lyn (Generex Biotechnology Corp.) showed that oralinsulin delivery appears to be safe, essential and successful.

- Oral-lyn insulin reaches the bloodstream quickly via the oral mucosa without deposition in thelungs
- It reduces the pain and inconvenience of multiple insulin injections throughout the day.
- The product also allows for precise dosage control and easy handling.
- Insulin oral spray have a rapid and a shorter duration of action compared to the regular insulintaken subcutaneously.[28]

Comparison between oral insulin and subcutaneous insulin in type 2 diabetes patients

A small observational study was done to compare oral insulin and subcutaneous insulin in volunteers.Ten male patients with type 2 diabetes participated in the study. They either took 300 units of insulin along with 400 mg of delivery agent orally or received 15 units RHI injected subcutaneously under controlled blood sugar conditions.

Tolerability of insulin inhalation

- The oral medication was tolerated fine by all the individuals.
- Still, 5 subjects complained of dizziness while consuming the spray.
- The dizziness reported by the subjects was mild to moderate and lasted for only about1-2 min.[29]

This study concluded with some inferences. Oral spray was rapid kick off action when compared toother route of administration whereas the volunteer's compliance was more.

CONCLUSION

Oral insulin exhibits rapid onset and a short-term action Moreover, it shows an elevated variability inabsorption between the individuals.

APPLICATIONS

1) Oral insulin is applied by using a spray that delivers the insulin directly into the mouth.
2) The insulin is simply sprayed onto the inner lining of the cheek, also known as the buccalmucosa.
3) It is a useful and painless alternative to subcutaneous injections, making it simple and smoothfor people to administer their insulin.
4) This method is helpful for individuals who may have difficulty with insulin injections.
5) It provides an alternative option that is more comfortable and less invasive.[30]

FUTURE PROSPECTIVE

A report cited the Hyderabad-based company as saying that the needle-free oral insulin spray called 'Ozulin' is set to hit the market in two-three years. Diabetes patients are likely to say goodbye to painful insulin injections with a Hyderabad-based company expecting to launch "oral form of insulin" by 2025–26. A painless shots of insulin is going to invade and becomes a revolutionary change where painful invasive methods which were there from past 80 years will be hopefully changed and more economical dosage from are seen in future.

CONCLUSION

Oral insulin spray is an exciting area research. It aims to provide a non-invasive method for delivering insulin. Researchers are working on developing formulations that can withstand digestion and effectively deliver insulin into the bloodstream. While it's still in the experimental stage. However, it's important to know that oral insulin spray is still being researched and isn't widely available yet. Scientists are working hard to ensure its safety and effectiveness.

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