Shree H. N. Shukla Institute of Pharmaceutical Education and Research, Rajkot

B. Pharm
Semester-VII

Subject Name: Novel Drug Delivery System
Subject Code: BP704TT

CHAPTER-2- Unit:2- MUCOADHESIVE DRUG DELIVERY SYSTEM

SYLLABUS:

Mucoadhesive drug delivery system:

Introduction, Principles of bioadhesion / mucoadhesion, concepts, advantages and disadvantages, transmucosal permeability and formulation considerations of buccal delivery systems

This subject is designed to impart basic knowledge on the area of novel drug delivery systems.

Learning objectives

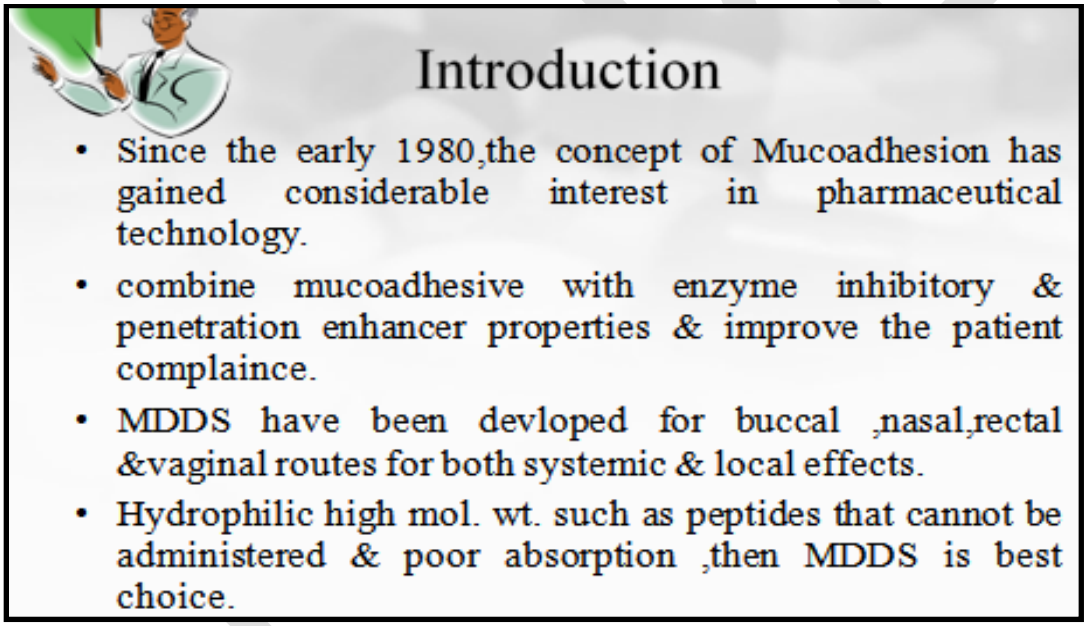
Upon completion of the course the student shall be able to

1. To understand various approaches for development of novel drug delivery systems.
2. To understand the criteria for selection of drugs and polymers for the development of Novel drug delivery systems, their formulation and evaluation.

Mucoadesive Drug Delivery System

What is Mucoadhesive Drug Delivery System (MDDS)

- Mucoadhesive drug delivery system interact with the mucus layer covering the mucosal epithelial surface, & mucin molecules & increase the residence time of the dosage form at the site of the absorption.
- Mucoadhesive drug delivery system is a part of controlled delivery system.



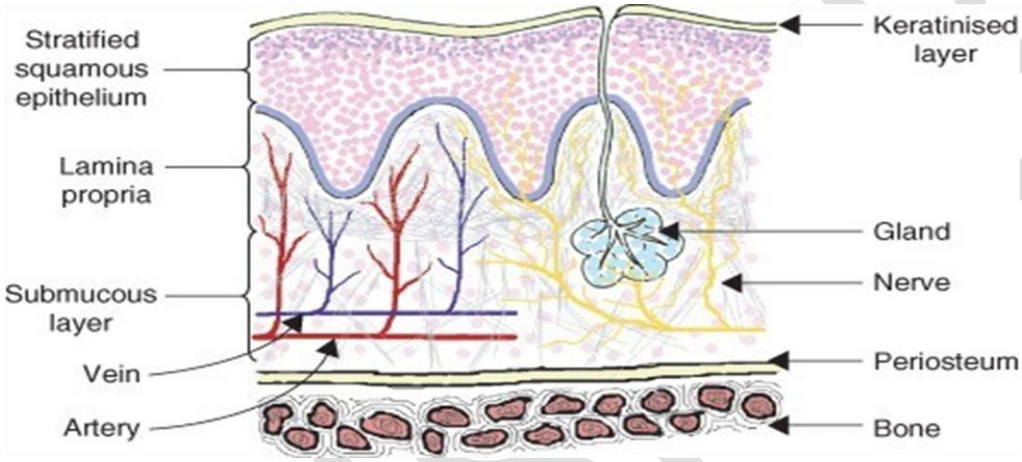
What is mucus?

- Mucoadhesive inner layers called mucosa inner epithelial cell lining is covered with viscoelasticfluid
- Composed of *water and mucin.* Thickness varies from 40 µm to 300 µm General composition of mucus

Water.....95%
Glycoproteinsand lipids.....0.5-5%
Mineral salts.....1%
Free proteins.....0.5-1%

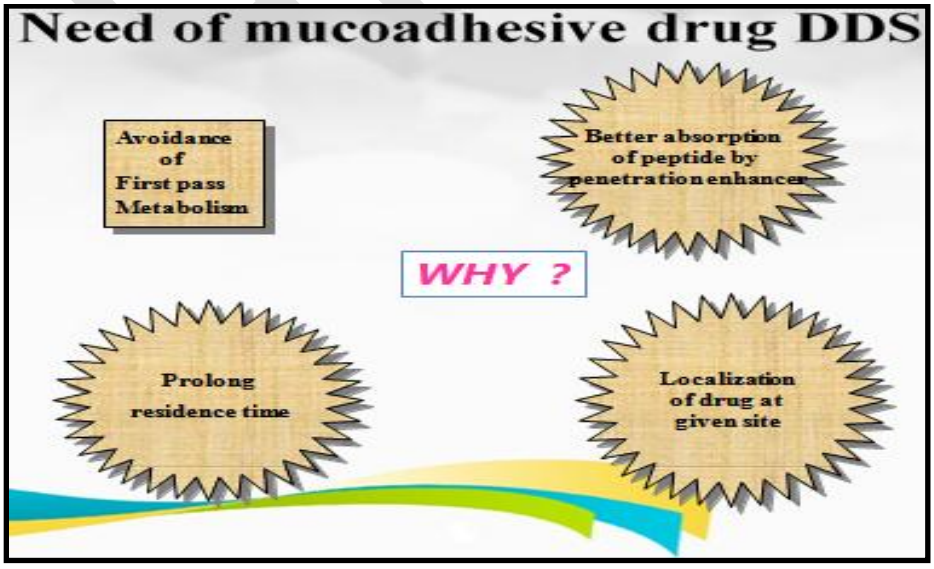
Muco	+	adhesive
- Inner layers called mucosa - Inner epithelial Cell lining Covered with viscoelastic fluid. -Secreted by Goblet cells -Composed of water and mucin -Other components include proteins, lipids and mucopolysaccharides ,electrolytes -Main role is protective and lubricates		-Tendency substance to remain adhered to surface -If substance adhere to Biological mucosal layers is called as Mucoahesion

General structure of mucous layer



Functions of mucus

- **Protective** : Particularly from its hydrophobicity
- **Barrier:** In tissue absorption of the drugs and influence the bioavailability.
- **Adhesion:** Mucus has strong cohesion properties
- **Lubrication:** keep mucosal membrane moist.



One Word Question Answer

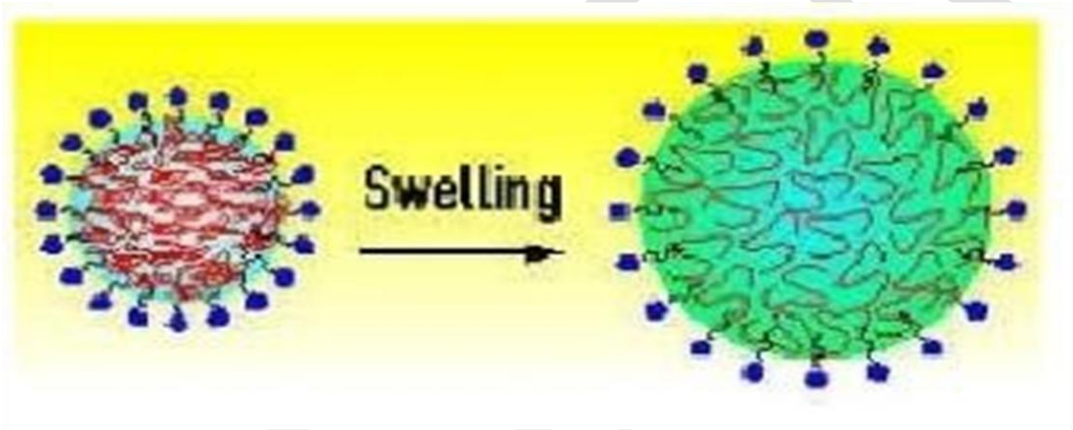
SR NO.	QUESTION	ANSWER
1	The system that interact with the mucus layer covering the mucosal epithelial surface, & mucin molecules & increase the residence time of the dosage form at the site of the absorption is called?	Mucoadhesive Drug Delivery System
2	Mucoadhesive inner layer is called?	Mucosa
3	The thickness of mucosa varies from?	40 µm to 300 µm
4	Which routes is used for systemic and local effect?	Nasal, Vaginal
5	Water and mucin is composition of?	Mucin
6	Which cell is produce the Mucosa?	Goblet cell

Mechanisms of Mucoadhesion

- The mechanism responsible in the formation of mucoadhesive bond
- Step 1: Wetting and swelling of the polymer (*contact stage)*
- Step 2 : Interpenetration between the polymer chains and the mucosal membrane
- Step 3: Formation of bonds between the entangled chains (both known as *consolidation stage)*

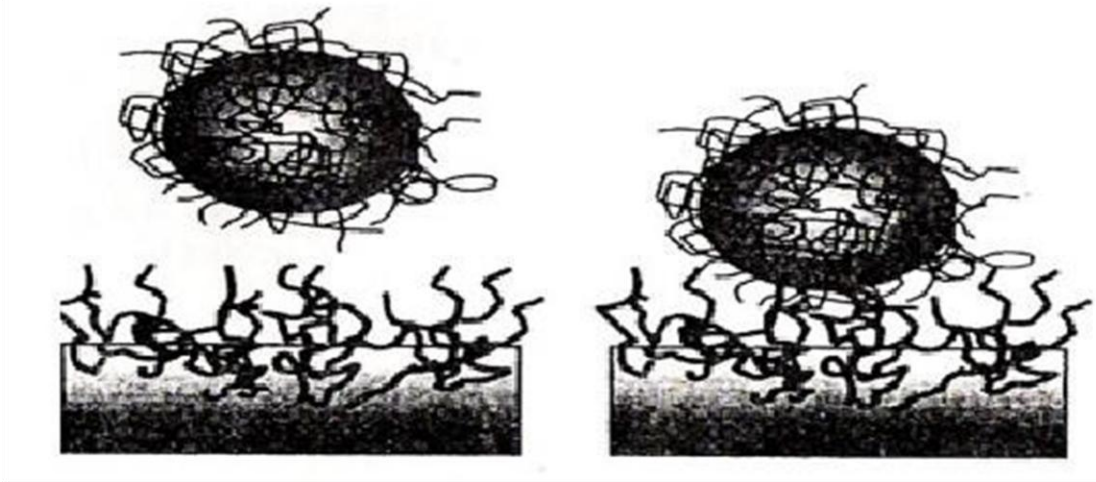
Step 1

- Wetting and swelling step occurs when polymer spreads over the surface of mucosal membrane to develop intimate contact.
- Swelling of polymer occur because the components of polymer have an affinity for water.



Step 2

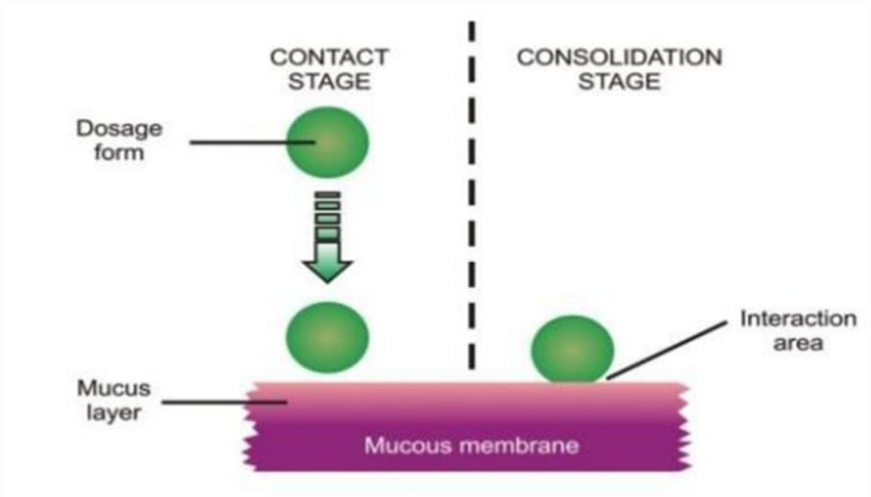
- In this step the mucoadhesive polymer chain and the mucosal polymer chains intermingle and entangles to form adhesive bonds.
- Strength of bonds depends upon the degree of penetration of the two polymer groups.



Interpenetration of mucoadhesive and mucous polymer chains

Step III

- This step involves formation of weak chemical bonds between the entangled polymer chains.
- Bonds includes primary bonds such as covalent bonds and secondary interactions such as vanderWaals and hydrogen bonds.



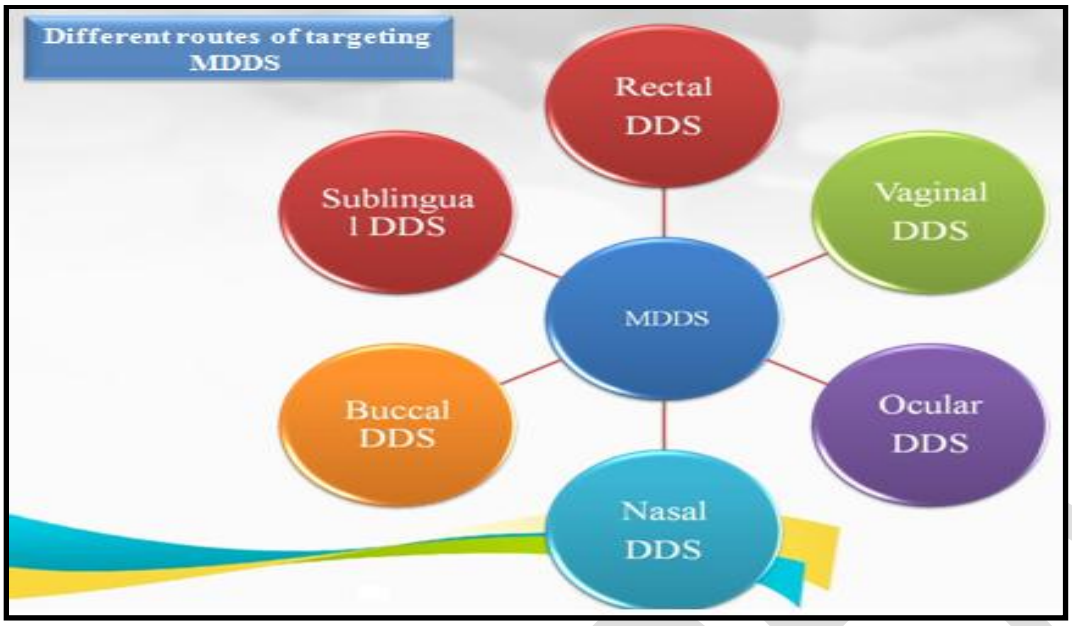
Theories of Mucoadhesion

- Electronic theory
- Wetting theory
- Adsorption theory
- Diffusion theory
- Fracture theory

1) **Electronic theory**
   -Attractive electrostatic forces between glycoprotein mucin network & the bioadhesive material.
2) **Wetting theory**
   -Ability of bioadhesive polymers to spread & develop intimate contact with the mucous membrane.
3) **Adsorption theory**
   -Surface forces (covalent bond, ionic bond, hydrogen bond & van der waals forces) resulting in chemical bonding
4) **Diffusion theory**
   -Physical entanglement of mucin strands and flexible polymer chains.
5) **Fracture theory**
   -Analyses the maximum tensile stress develop during detachment of the BDDS from mucosal surfaces.

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	First step of mechanism of mucoadhesion is called?	Contact stage
2	In which stage Wetting and swelling of the polymer occurs?	Contact stage
3	Which step is called consodilation stage?	Step 3
4	In which stage swelling of polymer occurs?	Step 1
5	In which stage Strength of bonds depends upon the degree of penetration of the two polymer groups.	Step 2
6	How many theories related to Mucoadhesion?	5



Mucoadhesive polymers

- They are water soluble and water insoluble polymers which are swellable networks joined by cross linking agent

Characteristic Of Ideal Polymer

- Degradation products should be non toxic and non absorbable from GIT
- Good spreadibility, wetting, swelling and biodegradable properties
- Optimum molecular weight
- Non irritant to mucous membrane
- Form a strong non-covalent bond with mucin epithelial cell surface

Polymer classification

A) According to their source

Natural and semisynthetic	Synthetic
Agarose	Carbopol
Chitosan	PVA
Gelatin	PVP
Pectin	Thiolated polymer
CMC	Methacrylic acid
Thiolated CMC	Polycarbophil
HPMC	
Hydroxypropylcellulose	

B) According to water solubility

Soluble	Insoluble
CMC, Sodium CMC, HPMC, MC, PVA, PVP, etc.	Carbopol, Polyacrylicacid,PEG, etc

C) According to charge

Charged	Uncharged
Aminodextran, Chitosan, Carbopol, SodiumAlginate, Pectin, SodiumCMC, etc.	Starch, PEG, PVA, PVP, etc.

Factors affecting mucoadhesion

A)Polymer related factors:

- Molecular weight
- Conc. of polymer
- Flexibility of polymer chains
- Presence of functional group
- Spatial conformation
- Cross linking density

B) Environment related factors:

- pH of polymer substrate interface
- Applied strength

C) Physiological factors:

- Mucinturn over
- Disease state

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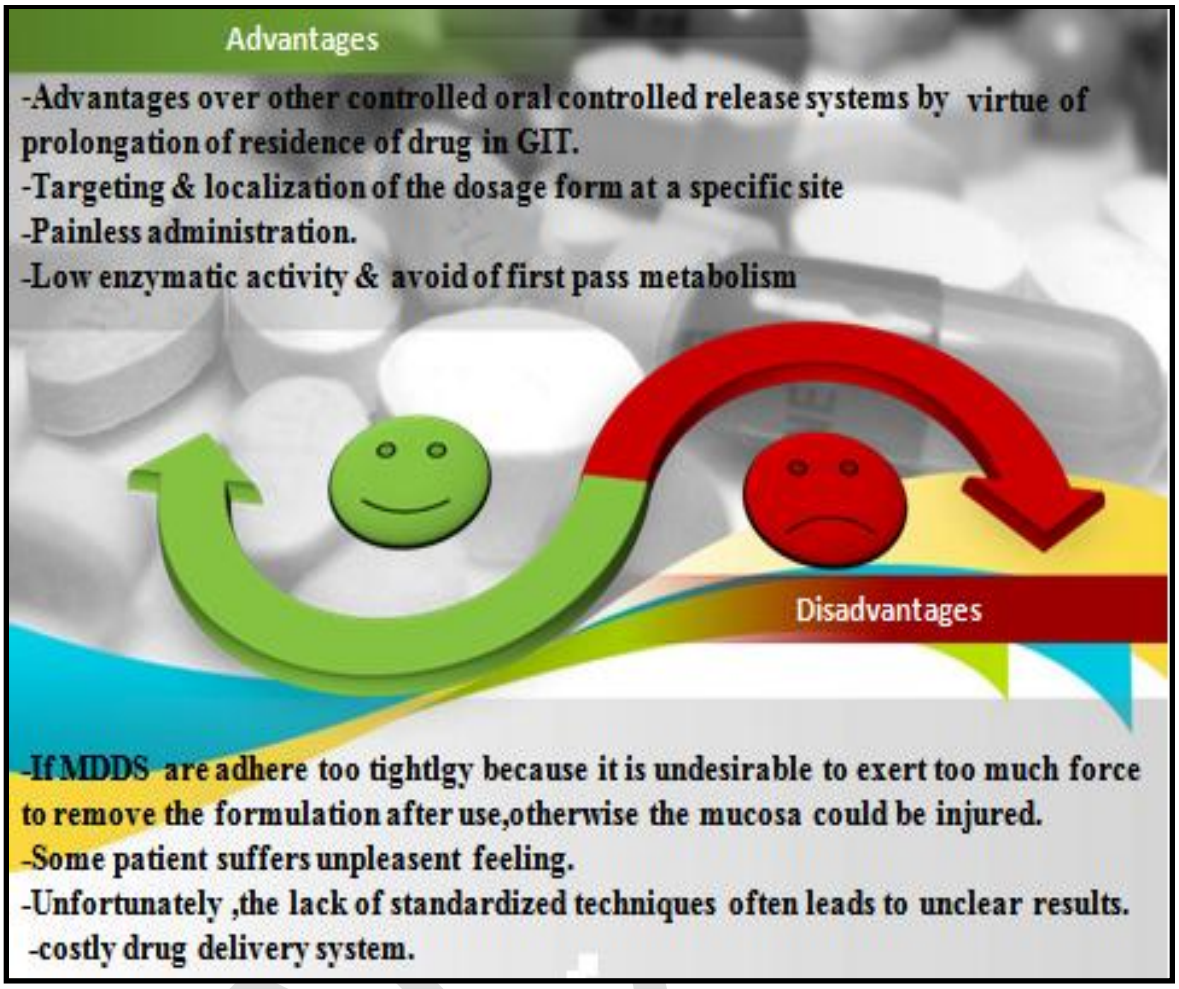
One Word Question Answer

SR NO.	QUESTION	ANSWER
1	They are water soluble and water insoluble polymers which are swellable networks joined by cross linking agent, this agent is called?	Mucoadhesive polymer
2	Which bond of mucoadhesive polymer is form with mucin epithelial cell surface	strong non-covalent bond
3	Solubilities of CMC, HPMC are?	Water soluble
4	Which polymer is called charge polymer?	Carbomer
5	Agarose and chitosan are example of?	Natural polymer
6	Rectal route is part of?	Mucoadhesive drug delivery syem



Buccal Drug Delivery system

Introduction: The delivery of drug into systemic circulation via buccal mucosa .i.e through inner lining through cheeks is called Buccal Drug delivery system. Such dosage forms are placed between cheeks and upper gums. Intended purpose of use is generally treatment of local or systemic conditions

WHY AND WHEN TO FORMULATE AS BDDS?

1. Some drugs have very short half-life and therefore need to be administered multiple times in a day. This reduces patient compliance.
2. Some drugs may undergo enzymatic degradation in GIT
3. Some drugs suffer great loss in bioavailability as they undergo first pass metabolism

Advantages

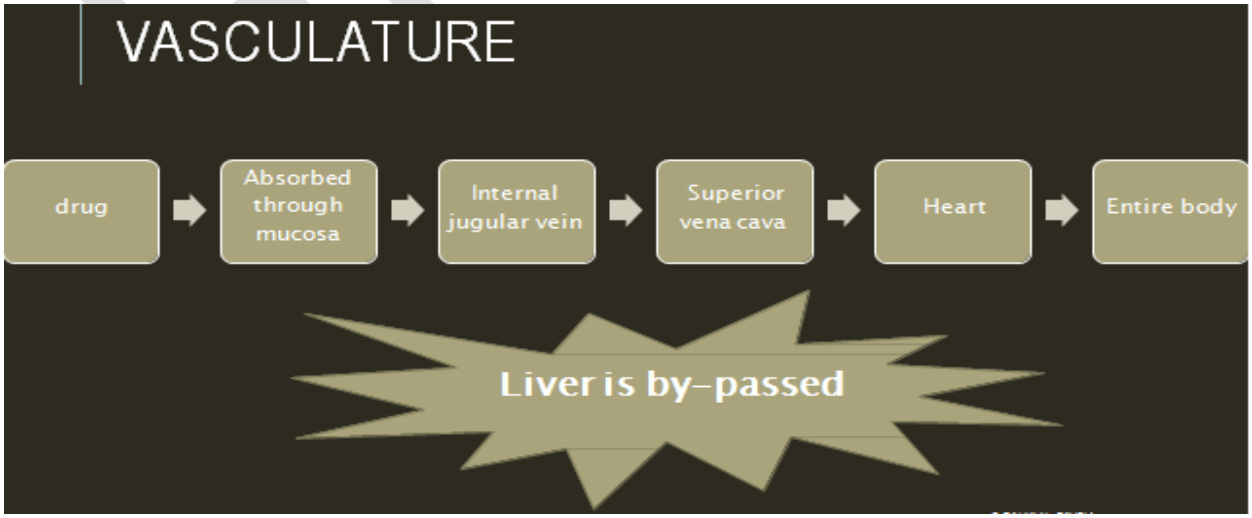
1. Easy to administer
2. Therapy can be stopped whenever required
3. For unconscious and trauma patients it is easy to administer
4. Bypass first pass metabolism
5. Drugs unstable in environment of GIT can be given through BDDS
6. Flexibility in physical state, shape, size and surface
7. Rapid onset of action

Disadvantages

1. Cannot administer drugs that are unstable at buccal pH
2. Not suitable for drugs with bitter taste, obnoxious odor, or irritant to mucosa
3. Only small dose can be administered
4. Eating and drinking may become restricted
5. Only those drugs that are absorbed via passive diffusion can be given through BDDS

WHAT IS THE ROLE PLAYED BY SALIVA ?

- Absorption of drugs through moist mucosa takes place more readily.
- Most drugs administered through BDDS are solids.
- They must be first dissolved before they can be absorbed.
- This is brought out by saliva



One Word Question Answer

SR NO.	QUESTION	ANSWER
1	The delivery of drug into systemic circulation via buccal mucosa .i.e through inner lining through cheeks is called.	Buccal Drug delivery system
2	Which dosage forms are placed between cheeks and upper gums.	Buccal Tablet
3	Which system is costly drug delivery system?	BDDS
4	Which route bypass first metabolism?	BDDS
5	What is half-life of drug that suitable for BDDS?	Short half-life
6	In which system eating and drinking may become restrict?	BDDS

Selection of DRUG for BDDS

I. MW should be less than 1000da
II. It should be having both nature i.e. hydro-lipophilic type
III. Should be potent {low dose so that formulation is not bulky}
IV. Non-irritant to mucosa
V. Drugs that degrades in GIT.

Ideal Features

- Non-toxic, non-irritant & pure.
- Good spreadibility, wetting, swelling, solubility & biodegradable if possible.
- Adhesion should be quick & with sufficient mechanical strength.
- Should have peel, tensile, shear strength.
- Should easily incorporate drug in formulation & it should not be obstacle in drug release.
- Cost effective.

Permeation Enhancer

- Permeation is very limiting factor in BDDS.
- Substances that facilities permeation through Buccal mucosa are called PE.
- Epithelium & Lamina Propria are very effective barrier to absorption. They should be used with very care & in optimum concentration (<1%), above this concentration toxicity due to membrane damage may occur & histopathological study should be done.

Mechanisms of Permeation's Enhancer

- Increasing fluidity & integrity of cell membrane.
- Extracting inter/intra cellular lipids.
- Altering cellular proteins.
- Altering mucus rheology.
- Acting at the tight junctions.
- Increasing thermodynamic activity of drugs.
- Surface tension decreasing.

Tablets

- It is small, flat, generally oval shape with 5-8 mm diameter.
- It is directly placed onto mucosal surface & adheres to it.
- We can get Unidirectional Release, Multidirectional release (as with conventional product).
- Generally, for unidirectional release, a backing membrane is applied, which is impermeable to liquid, to one side so that no drug release is

observed form that side & non-coated surface adheres to the Buccal mucosa. Ethyl Cellulose is used as backing membrane.

- Different marketed Buccal tablet
- Prochlorperazine maleate tab (Buccastem R M)
- Glycerl trinitrite Buccal tab (Suscord)
- Fentanyl Buccal tab (Fentora)
- Miconazole Buccal tab (Oravig)
- Testosterone (Striant) patented product

Transmucosal Permeation

- The transcellular and paracellular routes are involved in drug permeation across the epithelial membrane.
- In general, for skin and gastrointestinal mucosa viewed as lipodal barriers so partition coefficient and molecular size are important for diffusion.
- The same way recent study shows that the absorption of drug increases as the lipophiilicity of drug increase in the mucosa.
- It has been shown that ionic and lipid soluble compounds rapidly absorbed thorough rat rectal mucosa.
- The correlation between the rectal absorption and their partition coefficient proves the rectal mucosa as a lipoidal barrier.
- The study of vaginal absorption of straight chain alkanoic acids in rabbits, suggested that permeability coefficient increase as the length of alkyl chain increase but does not correlate linearly with their partition coefficient, indicating neither purely lipophilic nor pure hydrophilic nature.

Mucosal Absorption and Systemic Bioavailability of Drug

- The study on progesterone for pharmacokinetics and systemic bioavailability through oral and mucosal (nasal, rectal and vaginal) were compared in ovariectomized rabbits using radioimmunoassay.
- The result suggested that after mucosal delivery drug absorbed rapidly compared that with intragastric administration, where peak plasma concentration reached within 30 min.
- The pharmacokinetic analysis shows that the absorption rate constant Ka can be given as Nasal>Rectal>Vaginal>Oral.
- The data also indicate that a 3 to 10 times higher C max value and 5 to 9 times greater systemic bioavailability were obtained by mucosal drug delivery compare to oral administration of drug.

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	MW of drug for BDDS should be ?	less than 1000da
2	Substances that facilities permeation through Buccal mucosa are called?	Permeation enhancer
3	Optimum concentration of PE is?	(<1%),
4	Size of buccal tablet is?	5-8 mm diameter
5	Which type of release shows Buccal tablet?	Unidirectional
6	Which impermeable layer of buccal tablet is called?	Backing layer
7	The pharmacokinetic analysis shows that the absorption rate constant Ka can be given as	Nasal>Rectal>Vaginal>Oral
8	Transcellular and paracellular routes are involved in?	Transmucosal permeation