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REVIEW ARTICLE

Review on buccal drug delivery system

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ABSTRACT

Drugs can be delivered both systemically and locally through the oral cavity. Buccal drug delivery is a potential topic for further investigation with the goal of systemic distribution of orally ineffective medications as well as a viable and appealing alternative for noninvasive delivery of powerful protein and peptide therapeutic molecules. The oral route has long been the most convenient and widely used method of medication administration. The necessity for a safe and effective buccal permeation absorption enhancer is critical for the buccal medication delivery field's future success. The goal of a buccal drug delivery system is to accomplish site-specific drug release on the mucosa, which entails drug absorption across the mucosal barrier and into the systemic circulation. Absorption through the buccal mucosa prevents active drug loss due to presystemic metabolism by overcoming premature drug degradation caused by enzyme activity and the pH of the gastro intestinal tract. It is possible to produce fast acid hydrolysis and therapeutic plasma concentrations of the medication. Natural polymers have an important role in the pharmaceutical industry. Mucoadhesive polymers are used to increase drug delivery by increasing the contact time and residence time of dosage forms with mucous membranes.

INTRODUCTION

The oral method of medicine delivery is the most recommended by both patients and clinicians. The administration of drugs via a buccal drug delivery system is simple, and there is no risk of drug degradation in the hepatic first-pass metabolism or the gastrointestinal tract [1]. Drugs are taken by buccal route drug emptied into the internal jugular vein right away, and which is the pathway to gain entry into blood circulation [2]. In 1947 bioadhesive drug delivery formulations were introduced. To applyoral mucosa with penicillin gum tragacanth was combined with powdered dental adhesive [3]. Oral mucosal cavity is a viable and appealing location for systemic medication delivery of drugs, are categorized into three groups:

i) Buccal delivery: The mucosal membranes that line the cheeks are used to provide drugs.
ii) Sublingual delivery:Drugs are delivered systemically through the mucosal membranes that line the mouth's floor,
iii) Local delivery: Introduction of a medication into the mouth [1].

A mucoadhesive medication delivery method attaches to a mucus coat with an adhesive. Mucoadhesion is novel and developing drug delivery concept and maintains adhesion of the delivery system to the mucus membrane; The capacity to keep a delivery system in place for an extended period of time to ensure both systemic and local medication bioavailability [4]. Medication delivery method that adheres to the mucosa contains:

1. Sublingual drug delivery system
2. Buccal drug delivery system
3. Vaginal drug delivery system
4. Ocular drug delivery system
5. Nasal drug delivery system
6. Rectal drug delivery system

Natural polymers like chitosan are used. It is biodegradable and biocompatible, nontoxic polymer. Chitosan used as the permeation enhancer and enzyme inhibitor properties. Glucosamine and N-acetyl glucosamine make up chitosan [5].

Table 1: Natural polymer formulations for buccal dose forms

Sr. No.	Natural	Drug	Dosage form
1.	Gelatin	Aceclofenac	Mucoadhesive buccal
		Sumatriptan succinate	Mucoadhesive bilayered
2.	Guar gum	Diltiazem	Mucoadhesive buccal
3.	Sodium alginate	Methotrexate	Buccal mucoadhesive
		Diltiazem	Mucoadhesive buccal
4.	Chitosan	Metoprololtartarate	Bioadhesive bilayered
		Propranolol	Mucoadhesive buccal
		Cetylpyridinium	Mucoadhesive buccal
		Resperidone	Mucoadhesive buccal
		Salbutamol sulphate	Mucoadhesive buccal
		Verapamil HCL	Mucoadhesive buccal
		Propranolol	Buccal film
5.	Xanthan	Tizanidine	Mucoadhesive buccal

The Benefits of Using a Buccal Medication Delivery Mechanism [1, 6]

1. Buccal medication delivery has a high patient acceptance when compared to other non-oral methods of drug administration.
2. More accessible and richly vascularized for the management and disposal of dosage form.
3. In the gastrointestinal tract, acid hydrolysis is avoided. And by passing the first-pass effect.
4. The simplicity with which drugs are administered has improved.
5. Drugs are quickly absorbed into the venous system beneath the mouth mucosa because the buccal mucosa is heavily vascularized.
6. Improved patient compliance.
7. Drugs release for prolonged period of time.

Buccal Medication Delivery System Disadvantages [7, 8]

1. For both local and systemic action, patient tolerability in terms of flavor, mouth feel, and irritancy is a concern.
2. Some parts of the oral cavity may not receive effective doses of medications due to non-uniform dispersion of pharmaceuticals inside saliva after release from a semisolid or solid delivery mechanism.
3. Subsequent the drug's dilution due to continuous secretion of saliva.
4. Involuntary removal of dosage form and swallowing of saliva resulting in the loss of suspended or dissolved drug.

Buccal Medication Delivery System Limitation [9]

1. Drinking and eating restricted
2. This route cannot be used to provide drugs that have an offensive odour, bitter taste, or unpleasant taste, or that irritate the mucosa.
3. Passive diffusion is the only way to give drugs that are absorbed this way.
4. Drugs that are unstable at the pH of the buccal cavity cannot be given.

Polymers Used in Buccal Drug Delivery [10]

A] Natural Polymers:

1. Sodium alginate
2. Guar gum
3. Tragacanth
4. Gelatin
5. Chitosan
6. Xanthan gum

B] Synthetic Polymers:

1. Poly hydroxyl ethyl methyl acrylate
2. Poly ethylene oxide
3. Poly vinyl alcohol
4. Poly vinyl pyrrolidone
5. Cellulose derivative

i) Ethyl cellulose (EC)
ii) Methyl cellulose (MC)
iii) Hydroxy ethyl cellulose (HEC)
iv) Hydroxy Propyl Cellulose (HPC)
v) Hydroxy Propyl Methylcellulose (HPMC)
vi) Sodium Carboxy Methyl cellulose (NaCMC)

A Summary of Oral Mucosa

The mucosa of the mouth is made of stratified epithelium and it is outermost layer and lies in basement membrane. The deepest layer, the

lamina propria, is sub mucosa. The epithelium's composition varies based on the location in the oral cavity [3]. The masticatory mucosa has a cornified epithelium or keratinized epithelium within the oral cavity, and it is covered by stress-resistant regions such as the gingiva and hard palate [11]. Providing mechanical strength and chemical resistance it has four layers such as granular, keratinized, prickle- cell, and basal layer [11]. The hard and soft palates, the ventral tongue, the floor of the mouth, and gingival mucosa have a thickness of 100-200 m, whereas the buccal mucosa has a thickness of 500-800 m.

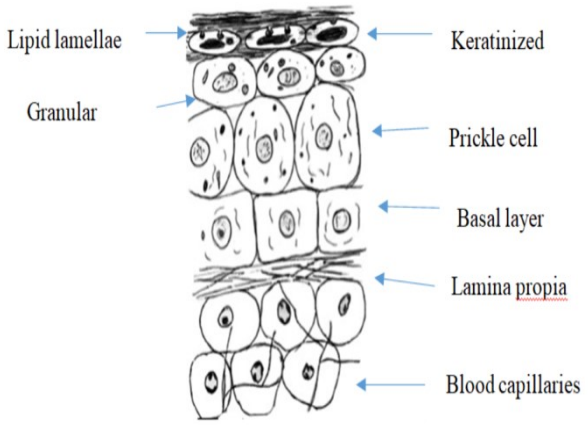

Figure 1: Structure of Buccal Mucosa

Role of Mucus

1. Cell- cell adhesion
2. Lubrication
3. Carbohydrates and proteins are found in it.
4. Mucoadhesive drug delivery system bioadhesion

Role of Saliva

1. Continuous mineralization of tooth enamel
2. Continuous demineralization of tooth enamel
3. Protective fluid for all mouth cavity tissue.
4. Oral mucosal dosage forms are hydrated [1].

Classification of Buccal Dosage Forms:

1. Buccal Mucoadhesive Tablets

It is a dry dose form that must be moistened before being applied to the buccal mucosa. Example: A double-layered tablet with a polyacrylic acid and hydroxyl propyl cellulose adhesive matrix layer and a cocoa butter inner core containing insulin and a penetration enhancer (sodium glycholate) [12].

2. Films and Patches

Buccal patches are made up of two laminates: a sticky polymer solution is cast onto an impermeable backing sheet, which is then cut into the desired oval shape. The film "Zilactin" is a new mucosal adhesive. And this "Zilactin," is made up of three organic acids in an alcoholic solution and hydroxyl propyl cellulose. The oral mucosa is covered with film, which is left in place for at least 12 hours. Even when confronted with a fluid [12, 13].

3. Semisolid Preparation (Ointment and Gel)

Patients accept bioadhesive ointment or gels less than solid bioadhesive dose forms, and this dosage form is exclusively utilised for localised drug therapy within the mouth cavity. Oral mucoadhesive delivery systems "Orabase" are made up of gelatin, pectin, and sodium carboxy methyl cellulose that are disseminated in a mineral oil gel base and poly (ethylene) and stay on the mucosal surface for 15-150 minutes [14].

4. Powder

When beclomethasone and hydroxy propyl cellulose (HPC) in powder form are sprayed onto the oral mucosa of rats, there is a considerable increase in residence time compared to an oral solution, with 2.5 percent of beclomethasone remaining on buccal mucosa after 4 hours [15].

Buccal Dosage Form Structure and Design

A. Matrix Type: Drugs, adhesive, and additives are combined together in the matrix arrangement of a buccal patch [16].

B. Reservoir Type: It has a compartment for additives and drugs that is separate from the adhesive. Control the drug's distribution path. The impermeable backing is utilized to limit drug leakage and decrease patch breakdown and deformation when in the mouth [16].

Buccal Absorption

When a dosage form is put in the outer vestibule between the gingiva and the buccal mucosa, drug release can occur [6].

Mechanisms

Passive diffusion of non-ionized species causes medication absorption through the oral mucosa; A process of the concentration gradient and

through the intercellular species of epithelium. The buccal mucosa has behaved predominately as a lipoidal barrier to the passage of drugs. Mucosa and (within limits) the more lipophilic (or less ionized) the drug molecule, it is absorbed. The major route of drug absorption for most of drugs is the passive diffuses in accordance with the pH partition theory of drug absorption [15].

E.g. Vitamins and sugars transported by a specialized transport system capable of saturation. The intercellular route, rather than the transcellular route, is the most common route for medication absorption. In intercellular route large hydrophilic molecules are transported [17].

Salivary secretion from drug solution alters buccal absorption kinetics by modifying the concentration of drug in the mouth, according to Dearden and Tomlison in 1971. The following is the linear relationship between salivary secretion and time.

$$\mathbf{Dm/dt =} \; Kc/V_i V_t$$

Where,
K – Proportionality constant
m– Mass of the medication in the mouth at time t.
c – Drug concentration in the mouth at the time
V_i – Amount of solution injected into the mouth cavity.
V_t– Salivary secretion rate [12].

Factors Affecting Buccal Absorption
The oral cavity is a complicated environment for drug delivery, with numerous dependent and independent variables that work together to limit the absorbable concentration at the absorption site.

Factors include:

A. Membrane Factor
B. Environmental Factors
    i) Saliva
    ii) Salivary gland
    iii) Movement of oral tissue [18].

Buccal Patches
Buccal patch is a non-dissolving thin matrix modified release dosage form made up of one or more polymer films or layers containing the medicine or excipients.

Patches have a mucoadhesive polymer layer that adheres to the gingiva, oral mucosa, and teeth, allowing for regulated medication release into the oral mucosa, oral cavity, or both. This patch is removed from the mouth and disposed of after a specified time [6].

Composition of Buccal Patches:
1. Active Pharmaceutical Ingredients (API)
Buccal film technology is vital for the delivery of a range of APIS. The size of the dosage form is limited, and high dose molecules in buccal films are difficult to include into buccal patches [12].

2. Polymers (Adhesive Layer)
Hydroxyethylcellulose, polyvinyl pyrrolidone, hydro propyl cellulose, polyvinyl alcohol, carbopol and other mucoadhesive polymers this polymers are used. And polymer swelling and hydration properties play important role. The hydration of the polymer causes an increase in mucous cohesive characteristics, which aids in mucoadhesion. Polymer chain flexibility and interpenetration between polymer and mucin chain interpenetration are important in swelling [19].

3. Diluents
Lactose DC has high aqueous solubility and it is selected as a diluent, its physic-mechanical properties and flavoring characteristics. And which is suitable for direct compression [20].
Examples: Starch, Microcrystalline [20].

4. Flavoring Agents:
Examples of flavor oils methanol, clove oil, peppermint oil, vanillin, spearmint oil, nut Meg oil etc [20].

5. Penetration Enhancer:
Examples: EDTA (Ethylenediamine tetra acetic acid), citric acid, cyno- acrylate etc [20].

6. Sweetening Agents:
Examples: Mannitol, aspartame, sucralose etc [20].

7. Plasticizers:
Examples: Propylene glycol, PEG100, 400, etc [20].

8. Backing Layer:
Ethyl cellulose, etc.

Methods for Improving Drug Delivery through the Buccal Route Include:

A. Absorption Enhancer

In absorption enhancer delivering compounds with a high molecular weight, example peptide, and has low buccal absorption rate [21].

Examples of Permeation Enhancer [21, 22]:

1. Aprotinin
2. Azone
3. Cetyltrimethyl ammonium bromide
4. Polysorbate 80
5. Polyoxyethylene
6. Phosphatidylcholine
7. Cyclodextrin
8. Cetylpyridinium chloride
9. Phospatidylcholine
10. Dextran sulphate
11. Sodium EDTA
12. Sodium glycolate
13. Sodium glucodeoxycholate
14. 2,3 Lauryl ether
15. Benzalkonium chloride

B. pH

The permeability of acyclovir in the presence of the absorption enhancer, sodium glycolate, at pH ranges of 3.3 to 8.8. The permeability of acyclovir *in vitro* is pH dependent with increase in permeability coefficient and flux at pH 3.3 and pH 8.8, and compared with mild range of pH 4.1, 5.8 and 7.0 [23].

C. Prodrugs

Bitterness prodrug versions of that drug, such as opoid agonists and antagonists, had reduced bioavailability as a prodrug. When given to dogs through the buccal mucosa, naloxone and nalbuphine are bitter medicines that produce excessive swallowing and salivation. Nalbuphine and Naloxone is administered in the prodrug form has no adverse effects and has bioavailability is 25 to 50% [24].

D. Patch Design

The pattern of drug release differed between multi-layered and single-layered patches. Some *in vitro* research was done on the type and amount of supporting materials used, as well as the drug release profile [21].

Bioadhesion:

A substance that is capable of interacting with biological materials and retained on them and holding together for increase period of time is called as bioadhesion.

Three types:

A. Cell adherence into culture dishes, as well as adhesion of various substances such as woods, metals, and synthetic materials, are examples of bioadhesion [23].

B. Artificial substance adherence to a biological substrate, such as polymer adhesion to soft tissue or skin [24].

C. Without involvement of artificial materials. A bioadhesion between biological layers and examples is cell aggregation and cell diffusion [25, 26].

Mechanisms of Bioadhesion:

Three phases are involved in the bioadhesion mechanism.

1. Close contact between a bioadhesive and a membrane results in good wetting of the bioadhesive and membrane, as well as bioadhesive swelling.
2. In the tissue penetration of the bio-adhesion take place.
3. Artificial materials are not involved. Cell aggregation and cell diffusion are instances of bioadhesion between biological layers and tissues.

Due to hydrogen bonding electrostatic interaction, hydrophobic contact, and dispersion forces, physical and chemical interactions result in the growth of the adhesive substance and chemical bonds [3, 27-28].

Theories of Bioadhesion:

1. Electronic Theory

Between the glycoprotein-mucin network and the bioadhesive substance, there are attractive electrostatic forces. Between the two, electrons transfer, generating a double layer of electric charge at the interface [23].

2. Wetting Theory

The ability of a bioadhesive polymer to create and spread intimate contact with the mucus membrane is required, and the polymer's spreading coefficient must be positive [23].

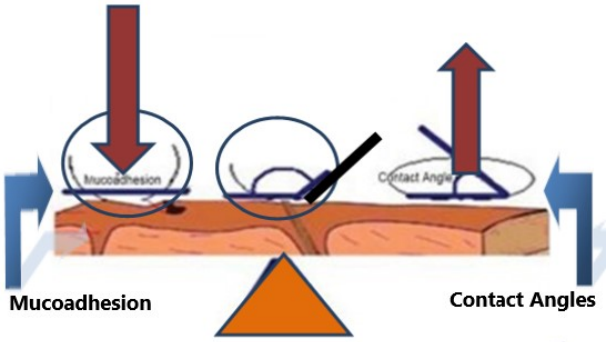

Figure 2: Wetting Theory

3. Facture Theory

The greatest tensile stress created during the detachment of the mucosal surfaces was examined. The strand and chain of the bioadhesive polymer mucin do not need to be physically entangled. And to look into the bioadhesion of rigid polymers that don't have a flexible chain [28].

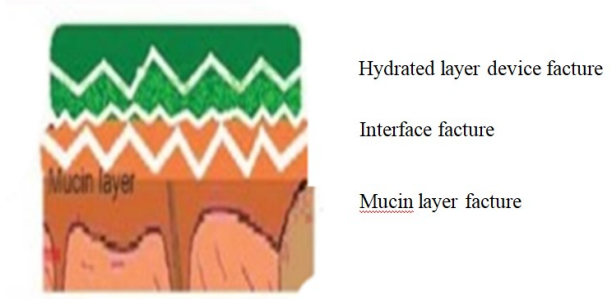

Figure 3: Facture Theory

4. Theory of Diffusion

Mucin strand and flexible polymer chain are physically entangled. Bioadhesive polymers and mucus glycoprotein have similar diffusion and solubility properties for greatest bioahesive strength and maximal diffusion and solubility [27].

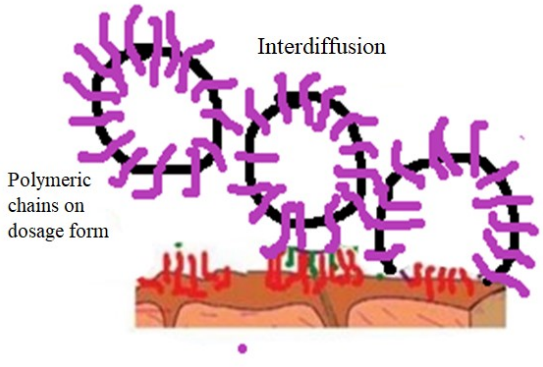

Figure 4: Secondary Interaction between Mucus and Mucoadhesive Device

5. Adsorption Theory

Chemical bonding results in surface forces. There are two kinds of chemical bonding. i.e. primary covalent and secondary chemical bonds including Vander- waals forces and electrostatic forces, hydrogen and hydrophobic bond [27].

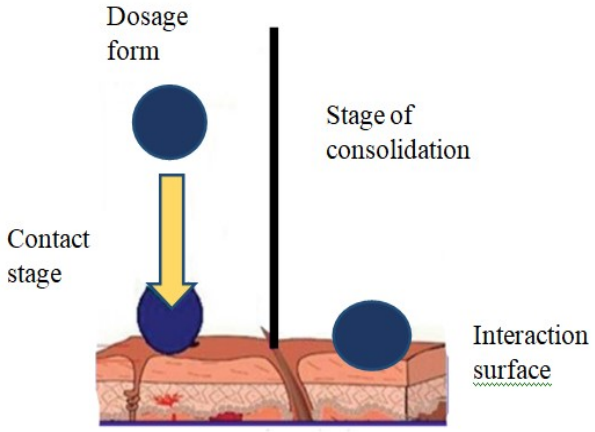

Figure 5: Process of Consolidation

Buccal Drug Delivery System Components:

A. Drug substance
B. Bioadhesive polymers
C. Backing membrane
D. Penetration enhancer

A. Drug Substance:

The selection of a suitable medication based on pharmacokinetic parameters is important in the design of buccal drug delivery systems.

The drugs have following characteristics [29].

1. Drugs with a biological half-life of 2-8 hours are ideal candidates for controlled drug administration.
2. The drug's standard single dose is quite tiny.
3. Drugs given orally T_{max} of the drugs shows wider – fluctuation or higher values.
4. Drugs given orally the drug absorption is passive [30].

B. Bioadhesive Polymers:

The initial stage in developing a buccoadhesive dosage form is to select and characterize bioadhesion polymers in the formulation. Bioadhesive polymers play a vital part in the buccal medication administration system. In matrix devices polymers are used. Some features of the polymers used in the buccoadhesive drug delivery method. It is simple to incorporate a

medication into a formulation. Polymers used for the buccoadhesive drug delivery system have some characteristics [31].

1. In corporation of drug into formulation is easy.
2. The polymers are easily available in market.
3. Environmentally friendly and inert.
4. The polymer and its decomposition products are non-toxic and can be absorbed through the mucosal layer [31].

Commonly Used Polymers Are
1. Natural polymers
EX. Sodium alginate, Gelatin

2. Synthetic and semisynthetic polymers
EX. PEG, PVA, HPMC, Carbomersetc [31].

C. Backing Membrane:
Bioadhesive devices are attached to the mucus membrane backing membrane. The material used as backing membrane should be impermeable to the drug, inert and penetration enhancer. Examples: Magnesium stearate, Hydroxypropyl methylcellulose (HPMC), HPC, CMC, Polycarbophil, Carbopoletc [32].

D. Penetration Enhancer:
Penetration enhancers are utilised in buccoadhesive formulations to promote medication release. They support in the systemic delivery of the drug by allowing the drug to penetrate into the viable tissue [33].

EX. Surfactant and bile salts, Sodium dodecyl Sulphate, Oleic acid, Cod liver oil, Capric acid, Chitosan, Trimethyl chitosan, Ethanol, Azone, Padimate [3].

Methods of Preparation of Buccal Patches:
There are two methods employed.
1. Solvent Casting
2. Direct Milling

1. Solvent Casting:
Drug is co-dispersed in an organic solvent and coated on a sheet of release liner in this method. After the solvent has evaporated, a thin layer of protective backing material is laminated to the coated release liner sheet and to form a film.

This method is simple but has some disadvantages, including high cost, long processing time and environment. The hot melt extrusion process can solve these difficulties [12, 26, 34].

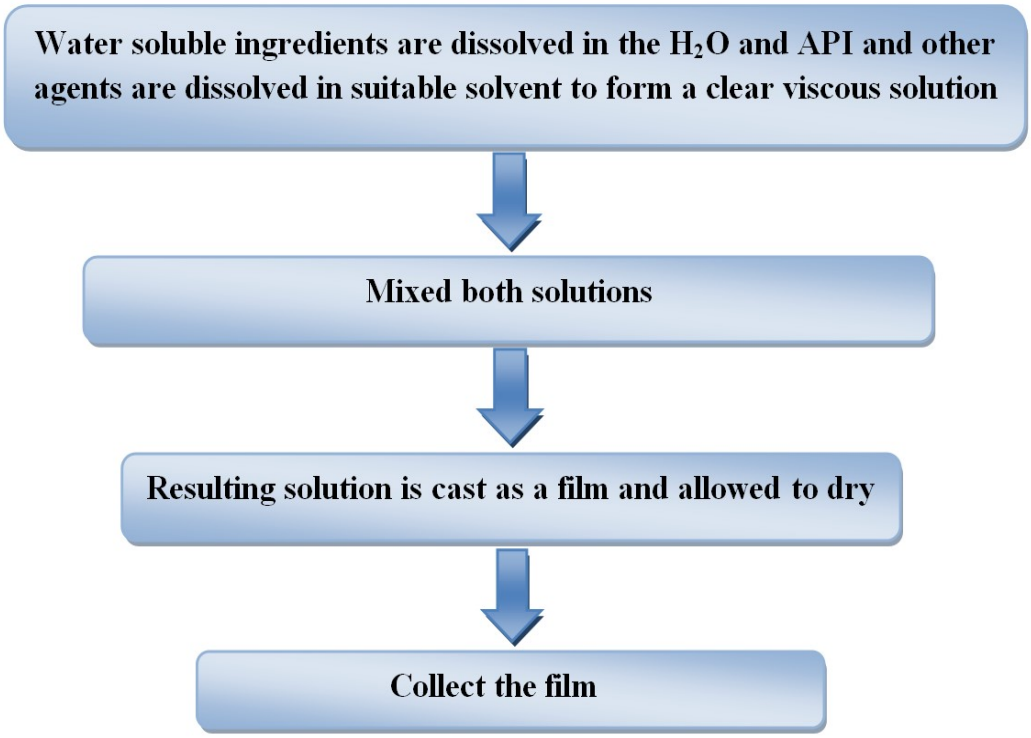

Figure 6: Solvent Casting Method

2. Direct Milling:
In this, without use of solvents patches are manufactured. That is patches are solvent free. Drugs and excipients are combined by direct grinding or kneading. There is no liquid present. Following the mixing procedure, the resulting material is rolled out on a release liner until it reaches the appropriate thickness. During the application phase, an impermeable backing membrane is used to control the direction of drug release, minimize distortion, and prevent drug loss and device disintegration [35].

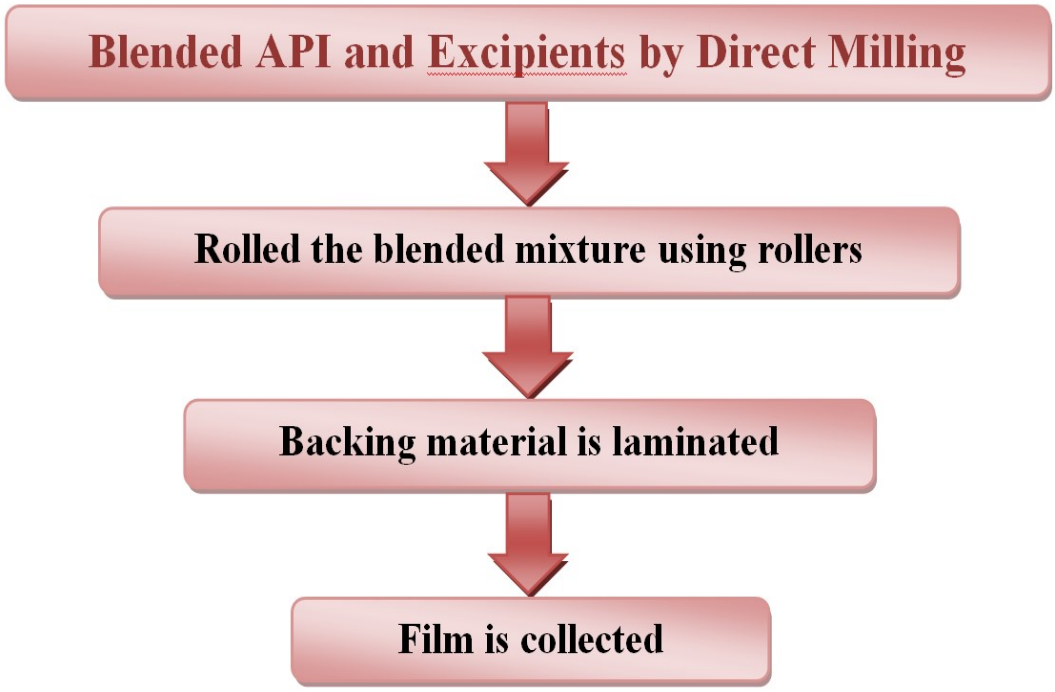

Figure 7: Direct Milling Method

List of Drugs Delivered by Buccal Route [12]**:**

1. Arecoline
2. Acitretin
3. Buprenorphine
4. Chitosan
5. Carbamazepine
6. Metronidazole
7. Nicotine
8. Oxytocin
9. Morphine sulphate
10. Omeprazole
11. Piroxicam
12. Ergotamine tartrate

Evaluation of Buccal Patch:

1. Surface pH
The pH of the buccal patch's surface was determined to see if any acidic or alkaline pH caused discomfort to the buccal mucosa *in vivo*. It was also decided to keep the pH of the surface as close to neutral as feasible. The electrode is a composite glass electrode. Buccal patches are swelled for 2 hours on an agar plate's surface. The pH of the surface of the swollen patch is tested using pH paper [36].

2. Swelling Study
Individual buccal patches are weighted and placed in a 2 percent agar gel plate. And this incubate at 37°C ± 1°C and examine the physical changes. Patches are taken from the gel plates at regular 1-hour intervals till 3 hours, and excess surface H_2O is filtered off with filter paper. Reweighed swollen patches (W_2) and swelling index (SI) is calculated by using formula [37]:

$$SI = \frac{(W_2 - W_1)}{W_1}$$

3. Thickness Measurement
Each film's thickness is measured at five separate spots using an electronic digital micrometer (Centre and four corners) [38].

4. Thermal Analysis Study
Differential scanning calorimeter (DSC) is used for thermal analysis [38].

5. Morphological Characters

Scanning electron microscope (SEM) is used for morphological characterization [38].

6. Palatability Test

Palatability test is used to determine palatability, which comes after physical appearance and bitterness. A, B, and C grades were assigned to each batch. When formulation scores one a grade formulation is average. When a formulation receives a score of two, it is deemed good, and when it receives all three grades, it is regarded very well [39].

7. *In- Vitro* Drug Release

The rotating paddle method of the United States Pharmacopeia (USP) XXIII was used to investigate drug release from bilayer and multilayered patches.

Phosphate buffer pH6.8 is considered as dissolution medium. The release was carried out at a temperature of 37°C±0.5°C, with a rotational speed of 50rpm.

The backing layers of buccal patches are attached to the glass disk with instant adhesion and the disk was allocated to the bottom of the dissolution vessel. And 5 mL sample withdraw at predetermined time interval and replace with fresh medium and the samples is filled by using a Whatman filter paper and analyzed after dilution by UV spectrophotometry at suitable nm [40-42].

8. *In – Vitro* Drug Permeation

The *in vitro* buccal drug permeation of drug through buccal mucosa (rabbit and sheep) was performed using a Keshary – Chien / Franz type glass diffusion cell at 37°C±0.2°C. Between the receptor and donor compartments, fresh buccal mucosa was placed. The core of the buccal pill was pressed against the mucosa, and the compartment was clamped shut. In the donor compartment, 1 mL of phosphate buffer pH 6.8 is added. And receptor compartment maintained by stirring with magnetic bead at 50rpm, at the predetermined time intervals. 1 mL sample can be withdraw and analyze drug content at suitable nm using UV spectrophotometer [12].

9. Study of Saliva Stability in Humans

The stability of a fast-dissolving film is tested in accordance with ICH recommendations. The films are examined for disintegration time, drug content, and physical appearance after predefined time intervals. The stability study of patch formulation was performed at 40°C, 37±0.5°C and 75±5% for 3 months. After 3 months, there were significant changes in the values of volume entrapment efficiency, percent drug release, and percent elongation after 8 hours [43].

10. *Ex Vivo* Mocoadhesion Time

The *ex vivo* mocoadhesion time was performed after the buccal patch was applied to freshly cut buccal mucosa (rabbit and sheep). Fresh buccal mucosa is wrapped on a glass slide, and then a mucoadhesive patch is wetted with 1 drop of pH 6.8 phosphate buffer and pasted to the buccal mucosa with fingertip gentle push for 30 seconds. The glass slide is placed in the beaker, which is then filled with 200 mL of phosphate bufferpH6.8 and held at 37°C±1°C. After 2 minutes, at a 50 rpm stirring rate, is applied to imitate the buccal cavity environment, and patch adhesion is measured for 12 hours. The time for changes in shape, color, collapsing of the patch and drug content is noted [44, 45].

CONCLUSION

For both local and systemic pharmacological activity, the buccal region provides a handy route of delivery. The buccal mucosa has a number of advantages over regulated medication administration over long periods of time. First-pass metabolism in the liver and pre-systemic clearance in the gastrointestinal tract, are avoided because the mucosa is well supplied with lymphatic and vascular drainage. Buccal mucoadhesive patches have lately acquired popularity in drug delivery. Natural polymers are increasingly being used in buccal drug administration, which is a potential topic for further research with the goal of systemic delivery of orally effective medications as well as a realistic and appealing alternative for potent peptide and protein therapeutic molecules. The requirement for a safe and effective buccal permeation absorption enhancer is critical in the field of buccal medication administration.

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