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A REVIEW ON RECENT ADVANCES IN EMERGING NANOPARTICLE-BASED BUCCAL DELIVERY SYSTEMS FOR ANTI-RETROVIRAL DRUG DELIVERY

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ABSTRACT: The development of mucoadhesive buccal formulations has recently gained a great deal of attention. Despite several proposed solutions, drug permeability and regulated drug release *via* this mode of delivery remain concerns for successful therapy. Clinical uses for recent advances in nanotechnology have been examined. In addition to ensuring effective distribution, the use of nanoparticles in dosage forms for buccal administration also helps to minimize any negative effects on biological systems. To load and distribute drug-containing nanoparticles to the buccal mucosa for topical and systemic applications, several strategies have been proposed. In order to improve medication delivery or targeting, this study outlines contemporary cutting-edge approaches for using nanoparticles in dosage forms. Of give a general overview of current approaches to implementing controlled drug delivery, these technologies are categorized and discussed. All of these noteworthy results will promote novel nanoparticle-delivered dose formulations for buccal distribution in clinical settings. Overall, the buccal mucosa provides a lot of advantages for controlled pharmaceutical delivery over an extended period of time.

INTRODUCTION: Several different layers of cells are located at the buccal mucosa, including stratum filamentosum, stratum distendum, stratum basale, stratum suprabasale, submucosa, and lamina propria. Because the mucosa and smooth muscle are largely static, buccal drug administration is advantageous due to patient compliance, simplicity of administration and removal, minimal enzymatic activity, and appropriateness for controlled release dose forms [1]. Drugs delivered buccally can be used for both local and systemic treatment. This kind of local therapy can maintain medication delivery at the intended spot while reducing unwanted effects. For systemic administration, the dosage form can avoid degradation or metabolism in the gastrointestinal tract (e.g., enzymes and high acidity in the stomach). The buccal mucosa is also an ideal site for drug absorption, with a long retention time for controlling drug release. Tremendous advances in buccal delivery dosage forms have been developed, e.g., films, patches, tablets, sprays, and chewing gum. Two main strategies are often used to promote the absorption of buccal mucosa: the adjustment of drug properties and the addition of a penetration enhancer in formulations [2].

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However, the limitations of overcoming drug solubility, drug permeability, controlled drug release and targeting remains a challenge, especially for poorly water-soluble drugs. To get around these restrictions for clinical applications, new strategies have been created. The inclusion of nanoparticles in dosage forms for buccal

medication administration has been encouraged by recent significant discoveries in nanotechnology. Additionally, nanoparticles have the capacity to transport large amounts of medication while shielding it from deterioration in bodily fluids. The buccal administration of solid and liquid formulations for local or systemic treatment has been studied. Moreover, both poorly water-soluble and water-soluble drugs can be applied in this system [3]. In this review, the overall advantages of and recent advances in using nanoparticles in buccal dosage forms will be discussed, allowing the selection of approaches as well as the future development of these dosage forms.

Advantages of Nanoparticles for Buccal Delivery: The use of nanoscale-based formulations is now one of the more impressive strategies in the enhancement of drug permeability *via* buccal administration. By encapsulating or coating the surfaces of nanoparticles, the dosage forms contain these nanoparticles and produce many advantages in drug delivery. For instance, a poorly water-soluble drug can be improved with drug solubility, drug dissolution rates or controlled drug release to enhance buccal bioavailability. Moreover, the nanoparticles can protect active pharmaceutical ingredients, leading to biocompatible and biodegradable dosage forms. Nanoparticles can also enhance the mucoadhesive behavior of dosage forms because their surface groups interact with the buccal mucosa via hydrogen bonding [4].

To get over these restrictions, the particle size is decreased to the nanoscale. Aggregation and inhomogeneous dispersion of big particles have the potential to impact mechanical films and mucoadhesive characteristics. However, the natural mucus barrier would be adhesive to nanoparticles, or the nanoparticles would be captured in this barrier, resulting in a rapid clearance or an inadequacy of these particles for reaching the target tissue to exert a medical effect. In order to potentially pass the mucosal barrier, the nanoparticles are therefore likely to be designed to do so, namely by avoiding mucin fibers and steric hindrance by the thick fiber mesh. These “mucus penetration nanoparticles” with controlled drug release properties at mucosal surfaces offer the improvement of therapeutic efficacy and minimization of side effects [5]. The size and charge of nanoparticles significantly affect the permeability. Data showed that the size of particles increases because of the protein-corona formation and agglomeration issues during their interaction with the mucus, and the particles at a size larger than 200 nm did not permeate the mucosa [6]. Additionally, cationic particles outperform anionic nanoparticles in terms of penetration through porcine buccal mucosa. In comparison to nanoparticles smaller than 50 nm, a 200 nm nanoparticle with a neutral charge demonstrated quicker and deeper penetration in areas of the buccal epithelium in a research [7].

Disadvantages of Buccal Drug Delivery: Despite the advantages, the buccal delivery has disadvantages and restrictions that hamper the drug delivery. Not all pharmaceuticals are appropriate for buccal distribution; for example, medications that are unsustainable at the oral pH, have a harsh taste or odor, or might trigger allergic responses should be eschewed. The absorption rate of the drug and its elimination by involuntarily swallowing of the delivery system and food or liquids ingestion, may decrease the amount of absorbed drug, decreasing the blood concentration which may not be enough to attain a therapeutic effect. The absorption rate of the drug depends on the surface area, the permeability coefficient and the drug concentration available in the oral mucosa surface.

The mouth cavity has a limited surface area that is available for medication absorption, about 50 cm^2 for the buccal mucosa and 27 cm^2 for the sublingual mucosa. Regarding the concentration of the drug available, it is important to understand the complex environment of the oral cavity, since there are several factors which reduce the drug absorption [8]. The most important impediment is saliva since it has a tendency to dilute medication concentrations at the absorption site, which results in low drug levels on the buccal mucosa's surface. Also, the swallowing of the saliva or the ingestion of food may cause the removal of the drug from the absorption site. This requires the patients to do frequent administrations of the drug to achieve the desirable therapeutic effect. Another important limitation is the irregular distribution of the delivery system within the mouth and the saliva. Additionally, oral medication distribution might be

hampered by talking, chewing, and eating, which can influence the release rates of the delivery system or retention durations [9]. As previously indicated, the buccal administration method might cause drug breakdown and reduce bioavailability. For example, the colon produces more P-glycoprotein than the buccal mucosa, but the cytochrome P_{450}-$3A_4$ is similarly expressed in the oral mucosa and in the small intestine, so it is an additional barrier to overcome by the new drug delivery systems administered through the buccal route. Another drawback is that the prolonged interaction of some drug delivery systems with the buccal mucosa may locally produce irritation and toxicity. Even though the oral mucosa is readily accessible, achieving a systemic effect by administering drugs topically is still unsuccessful because the mucosa also functions as a highly effective barrier to drug uptake due to its cellular and lipid composition, as well as the physiological factors that interfere with drug absorption. Overall, these drawbacks must be addressed and resolved by the new buccal drug delivery methods [10].

Buccal Drug Delivery Systems: The drug delivery systems for buccal administration should have high mechanical strength, high mucoadhesive properties, release the drug towards the mucosa in a sustained or controlled manner in order to avoid the drawbacks associated with buccal drug delivery, and high resistance to the flushing action of the saliva. Furthermore, the formulation should protect the drug from the oral pH and enzymatic degradation. These drawbacks could be eliminated by putting pharmaceuticals into polymer matrices such hydrogels, films, and nanoparticles.

Anionic and cationic polymers can be used to produce materials with mucoadhesivity and mechanical strength. Anionic polymers form hydrogen bonds with the hydroxyl groups of the mucin proteins to attach to them. For buccal medication administration, carboxymethylcellulose (CMC) and alginate are the two most often employed anionic polymers. The negatively charged components of the mucus interact with the cationic polymers to promote mucoadhesivity. The cysteine groups in the mucin and chitosan combine to produce thiol/sulfide linkages [11]. By using a multivariate design, authors created a thiolated N-dimethyl ethyl chitosan. As dependent variables, the tensile strength and bioadhesion force were examined. The study demonstrated that as the concentration of chitosan in the formulations increased, so did the tensile strength and bioadhesion force. The improved formulation had a bioadhesion force of 2.35 N and a tensile strength of 5.24 kg/mm^2. *Ex-vivo* investigations on permeation via rabbit mucosa revealed that the improved formulation also penetrated insulin at a greater rate than the N-dimethyl ethyl chitosan and chitosan nanoparticles [12]. To administer fluconazole to treat oral candidiasis, researchers created nanoparticles coated with chitosan and the cationic copolymer Eudragit. The zeta potential of the nanoparticles, which were around 200 nm in size, was +30 mV. The chosen formulation provided fluconazole topically to the oral mucosa of rabbits with *Candida albicans* infection, and after 3-5 days of formulation treatment, the oral mucosa had fully healed. Chitosan can be further thiolated to increase formulations' mucoadhesivity and, as a result, their bioavailability.

Additionally, nanoparticles can have enzyme inhibitors added to stop enzymatic breakdown. However, it has also been demonstrated that chitosan derivatives and polyacrylic acid reduce the enzymatic activity in the oral cavity [13].

Nanoparticle-delivered Mucoadhesive Films: Before becoming mucoadhesive films, nanoparticles often need to be loaded with a medication. A film is fabricated from a mucoadhesive polymer in nanoparticle formulations (e.g., nanofibres) or by the addition of mucoadhesive polymers.

Drug-encapsulated Nanoparticle Delivered Mucoadhesive Films: In this technique, a medication is first packaged into nanoparticles and then placed in films made of polymer. In fact, the nanoparticles are prepared in several steps, including nanoparticle separation, drug loading, lyophilization, and washing residual drug and polymer to produce dried nanoparticles for incorporation into mucoadhesive films. Various mucoadhesive films (e.g., hydroxypropyl methylcellulose in combination with Eudragit®, carboxylated chitosan, thiolated dimethyl ethyl chitosan, guar-gum) were investigated to carry drug-encapsulated nanoparticles for buccal delivery

[14]. The increased mucoadhesive property of films was demonstrated with the incorporation of liposomes in its structure. Additionally, flexible liposomes may enhance medication penetration into the buccal mucosa by swiftly altering shape in response to external influences. In a study of improving the delivery and permeation of vitamin B_6 via buccal delivery, liposomes containing water-soluble vitamins were incorporated into mucoadhesive film (carboxymethyl cellulose sodium and hydroxypropyl methylcellulose). In comparison to control films, the technology demonstrated efficient implementation of soluble vitamins with extended release and excellent permeability. Qingyuan used mucoadhesive buccal films (carboxymethyl chitosan) containing phospholipid-bile salt-mixed micelles for the administration of cucurbitacin B in an evaluation of poorly water-soluble drugs. This suggested approach demonstrated a higher release and a bioavailability boost around 10 times that of a typical film lacking nanoparticles in an *in-vivo* research [15].

Cationic polymeric nanocarriers can be used to archive high entrapment efficiency and increase penetration across the buccal mucosa. Electrostatic interactions between drug molecules and particles facilitate an increase in loading efficiency (e.g., carboxyl groups of heparin and quaternary ammonium groups of cationic polymethacrylate). Additionally, cationic nanoparticles interact electrostatically with mucus, replacing mucin on the particle surface and causing drug release. As a result, medication absorption is enhanced by a high concentration of the drug on the mucosal surface [16].

Coated Nanoparticle Delivered Mucoadhesive Films: It is possible to cover the surface of drug-loaded nanoparticles with mucoadhesive materials to further enhance the mucoadhesive capabilities of nanoparticles. For instance, curcumin-loaded polycaprolactone nanoparticles were coated with chitosan to prepare them for prospective buccal administration uses. The presence of chitosan on the surface of nanoparticles resulted in interacting with mucin through electrostatic forces. The interaction between the negatively charged mucosal surface and the positively charged nanoparticles (protonated amino groups) improved medication delivery when administered orally. For use with this method, the scientists developed mucoadhesive sheets with chitosan-coated nanoparticles (loaded with curcumin). Their results indicated that the prolonged delivery of curcumin was the main advantage of the proposed system [17]. In contrast to the above system, drug molecules can be coated onto the surface of nanoparticles before being incorporated into the films. Explorers suggested modifying an antisolvent co-precipitation approach to produce valine nanoparticles coated with insulin. These nanoparticles were then embedded in films for buccal delivery. Specifically, an increase in the addition of insulin resulted in smaller particle sizes (while 10% insulin reduced valine particles from 888 nm to 810 nm, 40% insulin substantially reduced valine particles to 323 nm) due to the stabilizing effect of molecules precipitating on the nanoparticles' surfaces, which stopped the formation of crystalline particles.

The advantage of coating active pharmaceutical ingredients on the surface of the nanoparticles was the achievement of a stabilized form of active molecules such as proteins and peptides without the presence of degradation products, even under high energy mixing (i.e., sonication). The proposed research explained that the insulin structure was maintained by the fast dehydration occurring by solvent displacement. A film with lysozyme-coated valine nanoparticles was shown to be effective for buccal distribution in a prior work conducted by the same team [18].

Nanofibre Delivered Mucoadhesive Films: Numerous uses of nanofibres in drug delivery have been made possible by the practicality of controlling the shape, porosity, and content of electrospinning fibers. Studies showed that nanofibres containing ketoprofen were appropriate for the local treatment of oral mucositis when administered buccally. In this study, ketoprofen was loaded in Eudragit L and Eudragit S nanofibres by electrospinning. The ketoprofen content of these nanofibres and casted films were equivalent. The efficiency of increasing the dissolution of a poorly water-soluble drug was demonstrated with the nanofibres, which could change the ketoprofen crystal state to an amorphous state. Therefore, the fast dissolution rate of ketoprofen (more than 80% after 50 min) led to a high drug concentration for the rapid diffusion of drug molecules.

In contrast, the casted films were unable to release drug until 300 min at pH 6.8 [19].

Multilayer Films Containing Nanostructure Materials: The development of sophisticated multilayer films has been reported in recent studies. This type of film contains 3 layers: a nanoparticle reservoir layer, a protective baking layer, and a mucoadhesive film layer. Actually, the foundation for this technique was the tri-layered buccal mucoadhesive patch, which consists of a dry, medicinal microtablet attached to a mucoadhesive film and a baked layer. Phenylephrine nanosuspensions were added to a microtablet in a subsequent study. This system was demonstrated to have relatively high permeability and was suitable for delivery of poorly water-soluble drugs [20].

The support of mucoadhesive films for tight adherence after application and the baking layer to stop nanoparticle dispersion away from the application site are the two obvious benefits of multilayer films containing nanoparticles. In addition, the nanoparticle in the reservoir layer has a role in controlling drug release or preventing drug particle size growth. For example, data demonstrated that the addition of carvedilol nanosuspensions to this system led to an increase in the medication's release rate *in-vitro* and an improvement in the bioavailability of the drug *in-vivo* in the rabbit model [21].

Similar to this, scientists created a three-layer system for vaccine distribution that included a nanofibre layer. Because the nanofibres have a wide surface area, a high loading of nanoparticles was introduced into the system. According to the findings, the barrier baking layer protected the nanoparticle reservoirs for precise drug delivery. Surprisingly, the scientists claimed that many kinds of nanoparticles, including virus-like particles, liposomes, lipid-based nanoparticles, and polymeric nanoparticles may be combined into nanofibrous materials for non-invasive mucosal treatments [22]. An electronspun layer was created and self-assembled into liposomes after coming into contact with water. These liposomes contained carvedilol. To put it another way, the multilayer film's nanofibre layer was created. To achieve great drug penetration, this nanofibre might, however, spontaneously assemble liposomes carrying carvedilol. Through buccal delivery, the study showed that this method might circumvent liposome constraints such short retention times and colloidal instability [23].

Nanoparticle Delivered Mucoadhesive Gels: To apply to the appropriate place for therapy in the event of a topical treatment, nanoparticles can be put in bioadhesive gels. It has been shown that solid lipid nanoparticles can deliver poorly water-soluble medications for topical treatment in a biocompatible and efficient manner. For the treatment of recurrent aphthous stomatitis, bioadhesive gel containing solid lipid nanoparticles containing cyclosporine A was employed.

Approximately 70% of cyclosporine A was located in the mucosa after 24 hours of treatment, indicating that the solid lipid nanoparticles containing the drug were localized in the buccal mucosa. Moreover, the *in-vivo* study showed an increase in the mucosal repair rate with the bioadhesive gel containing bioadhesive gel [24].

Curcumin, a medication that has limited water solubility, was also studied in combination with solid lipid nanoparticles in a mucoadhesive gel for topical application to the buccal mucosa. This study also indicated that a major amount of drug had accumulated in the buccal mucosa, and therefore, the gel loading solid lipid nanoparticles significantly reduced pain and completed healing of mucosal tissue after 6 weeks of therapy [25].

Nanoparticle Delivered Mucoadhesive Solid Matrix Forms: It is desired that nanoparticles be converted into solid dosage forms, such as sponges, wafers, or tablets for buccal administration, in order to further increase medication stability, patient comfort, and controlled drug release. For instance, compared to mucoadhesive gels, mucoadhesive tablets provide an extended residence period in situ and maintained medication release rate. In these designs, the nanoparticles must remain intact after condensing in solid forms to ensure drug stability, release rate, *etc*. Therefore, a cryoprotectant is usually utilized to protect nanoparticles during lyophilization [26]. In 2014, studies suggested that lyophilized naringenin-loaded monomethoxy poly (ethylene glycol)-poly (3-caprolactone) nanoparticles were compressed

into buccal tablets for the treatment of ulcerative diseases and oral inflammatory. Hydroxypropyl methylcellulose K4M or milk protein concentrate was investigated as a mucoadhesive polymer matrix for loading nanoparticles in tablets. The purpose of encapsulating naringenin in nanoparticles was its solubility improvement. The authors demonstrated that the compression of drug-loaded nanoparticles showed a faster drug release than a control tablet using pure drug with the same excipients [27].

Researchers used the direct compression approach to create buccal tablets using freeze-dried nanoparticles in an effort to create oral cancer treatments that incorporate nanoemulsions. The buccal tablets showed sustained drug delivery of the antiproliferative drug candidate. However, further investigations should be conducted to determine whether the compression process will not affect particle shape and size. Lyophilization is recommended for the preparation of buccal tablets in order to prevent the disintegration of nanoparticles. These solid matrix forms yield similar tablets; however, they are created by a freeze-drying process to sublimate the water/solvent from nanoparticles or gels to form tablets in a mould [28].

By lyophilization, for instance, solid lipid nanoparticles might be integrated into mucoadhesive polymers to create sponges or tablets. Explorers utilized a long mould to freeze dry solid lipid nanoparticles containing curcumin to form sponges. Specifically, glycerol and mannitol were necessary for flexible and elegant architectures, whilst polycarbophil or HPMC was utilized as a mucoadhesive polymer (i.e., glycerol as a plasticizer, and mannitol as a cryoprotectant). *In-vivo* results indicated that the residencetime was up to 15 hours with polycarbophil as the mucoadhesive polymer. Both glycerol and mannitol were optimized at 1% for the formation of elegant and flexible sponges [29].

In a later work, authors discussed the role of solid lipid nanoparticles on the formation of tablets and drug release. The authors used a round shape mould to create a tablet using lyophilization. The excess amount of solid lipid (stearic acid) in the solid lipid nanoparticles resulted in an increase in the particle size and a lower disintegration rate, which affected the dissolution rate. As a result, solid lipids play a prominent part in this form of buccal tablet. To delay medication release, a large concentration of solid lipids may be used. In contrast, an immediate drug release could be obtained by a sufficient amount of solid lipid. In addition to affecting drug release, a change in particle size due to the presence of solid lipids also affects the permeability.

The use of a small amount of solid lipid in the formulation led to wetter tablets and smaller particles of solid lipid nanoparticles, resulting in the significant penetration of the drug through the mucosa membrane compared to a large amount of solid lipid. The lyophilization strategy was also successfully used to incorporate microemulsions with an average droplet size below 200 nm. In this investigation, the ratio of oil to surfactant in the formulations had an impact on the physical quality and production of lyophilized wafers containing prednisolone loaded in microemulsions. While the low amount of solid surfactant (poloxamer 188) resulted in unsuccessful wafer formation, an excess amount of this surfactant led to a brittle wafer and a lack of flexibility. Furthermore, the creation of wafers with the proper hardness and a smooth surface was helped by formulations with high concentrations of oleic acid in microemulsions. The improved buccal wafer may be kept in the mouth cavity for up to 4.5 hrs, according to this *ex-vivo* investigation [30].

Lipid Based Nanoparticles: The drug dissolution in biologic fluids is one of the key factors for a high bioavailability. The absorption of hydrophobic drugs after oral administration is limited by the dissolution rate, which is the limiting step to attain high blood levels of the drug. Therefore, it could be smart option to transport medications in a lipid matrix with a large surface area for buccal administration in order to increase uptake and total bioavailability.

Because they are generally regarded as safe (GRAS), the lipids employed to make the nanoparticles have strong biocompatibility and tolerability characteristics. The lipid nanoparticles have been used to deliver drugs with a controlled release, mostly lipophilic drugs, since they are

relatively easy to produce with robust scale-up ability and, if properly tailored, can be targeted to specific tissues or organs. The high speed homogenization, sonication and high-pressure homogenization are the most common methods to prepare lipid nanoparticles. Although the high pressure homogenization technique is reliable and simple to scale up, the size of the lipid nanoparticles may be considerably polydisperse. While offering a smaller PDI, high-speed homogenization and sonication are more time-consuming and difficult to scale up [31].

The lipid-based nanoparticles may be classified into liposomes, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC), according to the type and/or blend of lipids used. Liposomes are generally composed by one (unilamelar vesicles) or more (multilamelar vesicles) bilayers with amphiphilic behavior, enclosing a hydrophilic core, and the phospholipids are the most common amphiphilic entrapping agents. Comparing SLN to liposomes, the lipid that makes up the core network of the SLN is solid at room temperature, enhancing both its durability and the efficacy of drug attachment. In addition, size dispersion and a longer prolonged release profile were two other SLN qualities that the NLC were created to enhance. The NLC are prepared using a blend of solid and liquid lipids, which may also increase the solubilization of loaded drugs. Additionally, the drug diffusion from NLC often exhibits biphasic behavior, with an early burst release followed by a later slower release of the drug due to the presence of lipids in various physic states. By adjusting the proportions of the liquid and solid lipids in NLC, it is possible to achieve better association efficiency and customized drug delivery kinetics. In the following subsections, it is addressed the different lipid-based nanoparticles for buccal delivery of drugs [32].

Buccal Delivery of Retroviral Drugs:

Buccal Films: Saquinavir can be administered buccally, which has the benefit of avoiding gastrointestinal enzyme breakdown and hepatic first-pass metabolism. Saquinavir's solubility in human saliva is pH-dependent and only moderately soluble. Increased saquinavir release from buccal formulations may be caused by decreasing microenvironmental pH (pHM) in saliva. The goal of the current study was to look at how organic acids affected the pHM, in vitro saquinavir release, and saquinavir's solid-state form. To measure pHM, a UV/Vis imaging technique was employed. pHM decreased from 6.8 to 5.4 after the malic acid-containing buccal films swelled for five minutes. Malic acid-containing films outperformed citric acid and succinic acid-containing films in sustaining low pHM. Due to the decreased pHM caused by the addition of organic acids, buccal films with acids released drugs more quickly than films without acids.

The rapid release of organic acids, however, restricted the augmentation of saquinavir release. Saquinavir didn't crystallize during its three months of storage at the increased temperatures (40°C) and high humidity (RH 75%) due to the addition of malic acid and citric acid, respectively. These findings imply that a pHM-modifying film formulation technique for saquinavir buccal administration is a viable option [33]. Lamivudine, an anti-HIV medication, has a poor bioavailability (62% in pediatric patients) and a short half-life (2 hr), necessitating repeated dosage. To get over these restrictions, buccal film studded with NPs was created for better effectiveness and longer medication release. The polydispersity index of the nanoprecipitated Lamivudine-Eudragit E100 polymeric nanoparticles was 0.315, and their average particle size was 338 nm. An early drug release of 49% was seen in buccal films created using the solvent casting process and containing sodium carboxymethyl cellulose (3:2) loaded with nanoparticles. This was followed by a continuous release that reached a high of 93% at the end of 8 hrs. SEM, thermal analysis, and crystal characterisation were used to validate the drug's encapsulation in the NPs and the film.

It was proven that the matrix system's Fickian diffusion mechanism allowed for sustained drug release. Particularly for pediatric anti-HIV medication, the improved formulation may be employed to improve therapeutic benefit at lower dose and side effects [34]. Only the oral method of administration is accessible for antiretroviral (ARV) medications like didanosine (ddI). By bypassing gastrointestinal degradation and hepatic first-pass metabolism, buccal delivery may increase bioavailability. In this investigation, buccal

administration of polymers with equal and opposing solubilities was attempted using homopolymeric and monolayered multipolymeric films (MMFs) containing ddI. A silicone-moulded tray with separate wells was used to create ddI-loaded monopolymeric films using hydroxypropylmethylcellulose (HPMC) or Eudragit RS 100 in various ratios. EUD films were made by emulsification casting/solvent evaporation, whereas HPMC films were made by casting/solvent evaporation. Through the processes of emulsification, casting, and solvent evaporation, MMFs made up of ddI: HPMC: EUD in various ratios were created. Drug content and drug release were used to describe the films (shaking water bath). SEM was used to analyze surface morphology and an electronic digital micrometer was used to measure the thickness of the film.

Films made only with ddI: HPMC (1:0.5) had immediate release profiles and were homogeneous. Only ddI: EUD (1:2.5) films had regulated release profiles and were homogeneous, elastic, and flexible. The addition of ddI to MMFs containing the drugs ddI: HPMC: EUD (1:0.5:2.5) and polymers with opposing solubilities produced homogeneous, elastic, and flexible films with instantaneous release profiles. The release profiles were regulated as the EUD concentrations were raised. The MMFs ddI: HPMC: EUD (1:0.5:2.5) had a drug content of 97.65%, were 2 cm2 in size, were 0.187 mm thick, and weighed 108.65 mg, respectively. Before dissolution, the films had a uniformly smooth surface that was compact, and after disintegration, textural alterations and pore creation were visible thanks to SEM. HPMC monopolymeric films can include ddI for applications requiring quick ddI release. For applications requiring regulated ddI release, homogeneous MMFs with drug and polymer (EUD) with opposing solubilities might also be created. It is possible to create MMFs with enhanced flexibility compared to monopolymeric films and quick and regulated ddI release patterns. The numerous films created for this study are suitable for ddI films' buccal delivery system optimization [35].

Liposomes Containing Buccal Films: One of the most harmful microbiological illnesses in the world is the HIV infection. This condition is brought on by the fast genetic diversity of HIV, which hinders the development of a vaccine. Numerous issues, such as the limited bioavailability and significant side effects linked to the current antiretroviral medications, usually hinder the use of antiretroviral therapy (ARVT) in the treatment of the disease brought on by HIV infection (ARVDs). This emphasizes the necessity of modifying medication biodistribution utilizing efficient carriers to alter the pharmacokinetic characteristics of ARVD. The same is true for several different disorders, where delivery methods can influence pharmacokinetic and dynamic features to decide whether a treatment is successful or not. Additionally, the mucosal linings of the oral canals provide a charming route of drug delivery that is systematic, boosting therapeutic efficacy and being frequently favoured by patients and practitioners.

Liposomes are small, spherical sacs made of phospholipid molecules and water droplets that were created to transport medications or other substances into tissues by interacting with and directing to certain organelles. As efavirenz (EVZ) is an ARVD model with low solubility and a number of adverse effects, this work concentrated on liposome production and liposomal buccal films (BFs) for prospective buccal distribution of EVZ. Utilizing crude soybean lecithin (CL) and cholesterol, the liposomes were created using the thin film hydration technique. Particle size, Zeta potential, shape, encapsulation efficiency (EE%), and release kinetics investigations of EVZ-loaded liposomes were all assessed.

Utilizing DSC, XRD, FTIR, and EDS, the physiochemical characteristics of the liposomes were also assessed, and the formulation with the highest encapsulation efficiency was chosen as the solvent medium for the formation of the buccal film. The liposomal suspension served as the dispersion medium when the buccal films were created utilizing the solvent casting technique. Using a digital Vernier calliper (DVC) and a digital weighing scale, the films' physical characteristics (thickness, weight fluctuation, and folding endurance) were improved. XRD, DSC, FTIR, TEM, EDS, and SEM were used to further investigate the physiochemical characteristics of the chosen BFs films formed of Carbopol (CP) and its combination with Pluronic F127 (PF127).

The use of a Franz diffusion cell was used to examine the permeation research of the chosen BFs. The films comprised of other polymers (HPMC) alone or in combination with PF127 showed much worse bio-adhesive capabilities than the BFs built of CP alone or its combination with PF127. With a CL to cholesterol mass ratio of 1:1 and a total lipid to drug mass ratio of 2:1, the developed liposome formulation demonstrated high encapsulation of 98.8%. These liposomes were discovered to be well suited for targeted distribution to the HIV-infected cells due to their average particle size of 104.82 nm and Zeta potential of -50.33 mV. The CP-based BFs (without and with PF127) showed acceptable flexibility values of 258 and 321 and somewhat acidic pH values of 6.43 and 6.32, as well as good film thicknesses of 0.88 and 0.76 mm, 68.22 and 86.28 mg, and all of these characteristics. It was discovered that the swelling percentage for CP film alone was 50% and for CP film combined with PF127, it was 78%. Over the course of 24 hrs, the total quantity of medication that penetrated through the buccal epithelium from CP film alone and CP film plus PF127 was approximately 66% and 75%, respectively. Additional research into the encapsulation and delivery of EFV-like antiretrovirals for improved solubility, site targeting, and prolonged release using mucoadhesive polymers and crude soybean lecithin, which holds some added economic values as naturally occurring lipid and polymeric mixtures as a promising delivery system for buccal delivery of ARVDs, is being done [36].

CONCLUSION: The buccal mucosa provides a lot of advantages for controlled pharmaceutical delivery over an extended period of time. The mucosa is sufficiently supplied with both vascular and lymphatic drainage, preventing first-pass metabolism in the liver and presystemic clearance in the digestive system. The patient appears to think it's a good idea, and the position is perfect for a retentive device. With the right dosage form design and formulation, the permeability of the mucosa and the surrounding environment may be maintained and modulated to facilitate medicine absorption. The objective of continuing research on buccal drug delivery is to provide a practical and attractive replacement for non-invasive administration of potent peptide and protein therapeutic agents as well as systemic distribution of drugs that are inefficient when taken orally. For a potential future in the field of buccal medication administration, however, the requirement for secure and efficient buccal permeation/absorption enhancers is essential.

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