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A STUDY ON FORMULATION AND EVALUATION OF BUCCAL FILMS OF NATEGLINIDE

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ABSTRACT

Numerous illnesses, whether acute or chronic, are typically treated with the aid of a drug delivery system and particular dose forms. The oral route is one of the several delivery methods for medication that is ideal and preferred by patients. For some medications, the oral route causes issues. Several factors, including the location of the enzymes in the GI fluids, the pH of the GIT, and the enzymes attached to the GIT membranes, may contribute to bioavailability issues. In some instances, the mechanism or the route of administration can be changed to address drug-related issues. The development of new drug molecules entities to the unique delivery method of already existing drug molecules up to certain extending changes their therapeutic efficacy, patient protection, and prevent unwanted consequences were the key study areas. Using powerful pharmaceuticals is one of the much technological advancement that is essential to a healthy living. Notwithstanding its safety and pharmacological efficacy, the idea of a dosage form in which a medicine is incorporated is effectively evolving. Drug delivery systems have been designed using a variety of scientific technologies. Due to its superior accessibility, pleasant dosage administration, and patient compliance for non-invasive medication delivery, oral drug administration is significant and frequently employed. Oral dosing forms have some drawbacks, including uneven medication absorption, brief stomach residence duration, and partial drug release. To get over these restrictions, a lot of focus has recently been placed on adapting oral dose forms to survive in diverse GIT environments. Although the relationship between medication administration and its pharmacological effect is a complex parameter, choosing and formulating the optimum dosage form is an essential step in the drug development process. Each drug response is affected by a number of intrinsic and extrinsic factors, including product bioavailability (drug absorption rate), pharmacokinetics, and the specific concentration-effect connection.

KEY WORDS: **Formulation and Evaluation, Buccal Films, Nateglinide, Buccal Mucosa.**

INTRODUCTION

Transepithelial drug administration through the skin or absorptive mucosa appears to have numerous advantages over oral drug delivery, including better bioavailability and the potential to administer smaller dosages of medication with fewer dose-related side effects. Transdermal delivery systems are slower than transmucosal delivery techniques in terms of delivery speed. Additionally, since delivery takes place in a tissue that is both less patient-specific and more porous than skin, there is less between-subject variability. Additionally, these methods may be employed to administer medications whose bioavailability is weak or inconsistent due to high hepatic first-pass metabolism. The buccal, sublingual, palatal, gingival, nasal, pulmonary, rectal, vaginal, and ocular channels are among the absorptive mucosae. On the other hand, the availability of a very limited surface area for absorption as well as the high variability in mucus secretion could have a significant impact on drug absorption in the case of nasal delivery. Additionally, extreme medication sensitivity results in considerable, irreversible mucosa damage. Although there is a large surface area accessible for absorption during pulmonary delivery, the main problem is repeatable drug placement in the alveolar region because of mucociliary clearance, making it unsuitable for sustained delivery. Vaginal, rectal, and ocular mucosae are viable sites for local rather than systemic treatments due to their many benefits but low patient compliance. Although more permeable, sublingual mucosa is not appropriate for retentive administration. Although the palatal and gingival channels have a low permeability coefficient, they are suitable for retentive drug administration.

The buccal cavity was discovered to be the most practical and accessible site for the local or systemic distribution of medicines among all transmucosal sites. It is extremely promising for the delivery of medications with low oral bioavailability due to its expanse of relatively static smooth muscle, extensive vascularization, and direct access to the systemic circulation through the internal jugular vein. Other notable and meritorious benefits of buccal adhesive systems include easy formulation removal, improved patient compliance, and higher patient acceptance.

STRUCTURE OF THE BUCCAL MUCOSA AND ITS APPLICABILITY

The buccal region is the area of the mouth that is limited on the sides by the lips and cheeks, above and below by the mucosal reflections from the lips and cheeks to the gums, and posteriorly and medially by the teeth and/or gums. The submucous tissue of the cheeks contains a significant number of racemose, mucous, or serous glands.

Blood is supplied through the maxillary artery, where blood flow is richer and faster (2.4 ml/min/cm2), allowing for passive drug molecule diffusion over the mucosa. The buccal epithelium is thought to change every 5 to 6 days. Due to the near absence of Langerhans cells, buccal mucosa is more resilient, porous, and tolerant to possible allergens than other mucosa and skin. There is practically little enzymatic activity in buccal mucosa. The buccal mucosa's permeability was calculated to be between four and four thousand times greater than that of the skin.

Buccal mucosa is made up of numerous layers of various cell types. The epithelium is around 40–50 cell layers thick and is stratified, like the squamous epithelia seen in the rest of the body. The nonkeratinized stratified squamous epithelium known as lining epithelium has a surface area of 50.2 cm2 and a thickness of roughly 500–600 m. Submucosa, lamina propria, and the basement membrane are all present beneath the epithelial layer. Blood veins and capillaries abundant in the lamina propria that open to the internal jugular vein. According to a lipid examination of buccal tissues, phospholipids make up 76.3%, glucosphingolipids make up 23.0%, and ceramide NS makes up 0.72%. Ceramides such Cer AH, Cer AP, Cer NH, Cer AS, and EOHP/NP, as well as acyl glucosylated ceramide, are completely absent.

DRUG DELIVERY SYSTEMS IN BUCCAL FORM

The buccal mucosa is a potential location for sustained release delivery systems that could maintain a consistent flow of medication in the systemic circulation due to its histological characteristics. To transport medications into the oral cavity for either local or systemic action, a variety of delivery techniques have been devised. Mouthwashes, lozenges, gels, chewing gum, lollipops, films, patches, pills, and a few specialist transmucosal devices are among them.

Lozenges and mouthwashes are the simplest and oldest dose forms. The medication is continuously removed from these non-attached delivery systems by a sizable volume of saliva, causing an initial burst effect followed by a swift fall in concentrations to below therapeutic levels. For better patient compliance, the dosage form must also be pleasant.

The salivary scavenging effect could not be countered by common gels, pastes, or even dosage forms for prolonged release through buccal mucosa such medicated chewing gum, lollipops, and lozenges. To get around these restrictions, delivery systems built on the idea of bio/mucoadhesion and intended to stay in the buccal mucosa for extended periods of time have been created.

RESEARCH METHODOLOGY

RAW MATERIALS SELECTION AND COLLECTION

Drugs and polymers were gathered from various firms, and they had to be evaluated for organoleptic features like colour, taste, and flavour as well as physical properties like solubility, melting point, and loss on drying.

CHARACTERIZATION OF NATEGLINIDE

Many techniques, including UV spectroscopic technique, IR study, and differential scanning colorimetric approach, were used to characterise the active medicinal ingredient.

FORMULATION & EVALUATION OF BUCCAL FILMS

The buccal films of Nateglinide were prepared by solvent evaporation method.

FORMULATION OF BUCCAL FILMS

In 70% ethanol, the observed amounts of polymers were dissolved. The carbopol polymeric solution was neutralised using triethanolamine. After levigation with 30% weight-for-weight propylene glycol, precisely 20 mg of the medication were added to the polymeric solution. To get a consistency resembling glue, the solution was occasionally mixed. The mixture of medication and polymer was placed onto a petridish and left aside for a week to allow the dissolvables in the mixture to dissipate. Next, following a thorough examination, the dried

patches were removed, checked for air pockets, and specific breadth films were generated using an incredibly made round stainless steel cutter.

RESULTS AND DISCUSSION

The Nateglinide film was produced using the solvent evaporation process. In this method, buccal films were produced using a "O"-shaped ring that was mounted on a glass surface. Several amounts of polymers, such as HPMC, chitosan, carbopol, and PVP, were added to this. The solvent chosen at that time was ethanol (70% v/v). Despite this, a plasticizer called propylene glycol is also included as a penetration booster.

PHYSICOCHEMICAL EVALUATIONS

The buccal films were even in thickness and smooth; there were no obvious breaks or overlaps in the bulk. The results of the evaluations of the films' various physical and chemical properties are shown in table-1. The films produced with de-ionized water and ethanol showed excellent mechanical quality. This is due to the high rate of ethanol volatilization, the majority of which occurred when the film dried. Trials were conducted using various solvent composition rates, and it was found that lower concentrations indicated considerable lengthening and, at the very least, limited flexibility. Films made with high concentrations of ethanol and increased concentrations of propylene glycol and water were more durable than those made with only those two substances. Hence, a higher concentration of ethanol may shorten the drying process and have an impact on the structure of films. 70% v/v ethanol, 30% propylene glycol, and refined water were selected from the results above.

Given the quantities of the polymers used, such as HPMC, chitosan, and carbopol, the films' physicochemical characteristics showed significant variation. Then, using an electronic scale and vernier callipers, the weight and thickness of three films of each Nateglinide formulation were taken and measured. The findings showed that the films' weights varied from 165.17 mg to 178.23 mg while their thicknesses varied from 0.32 mg to 0.48 mg. It was concluded from the results above that when the concentration of chitosan, carbopol, and HPMC increases, so do the film weight and thickness. The results are listed in table-1.

Collapsing folding endurance was seen to exceed 300 times in each of the flicks. Our estimates of endurance showed that the films were suitable for ingestion with a sufficient

amount of medication. All of the films that were produced were excellent, adaptive, and stylish, and they ranged in length from 2814.037 to 3205.013. Carbopol was frequently employed to create the flexibility and delicacy that could be recognised by its extremely cross-connected conformation. The film (NF10) showed the best ability to fold. Each film's surface had a pH between 6.60 and 6.81, with a pH range of 0.015 to 0.01. The results demonstrated that there was no actual variation in the surface pH of the entire films, and that the pH range within the buccal cavity is the same (pH 6.5 to 6.8). As a result, it was concluded that films do not cause discomfort while organisation and support result in tolerant consistency.

In order to ensure the physical strength of the films and to further evaluate their dependability and trustworthiness in dry conditions, % moisture absorption and % moisture loss tests were conducted on them. The moisture absorbed as far as rate in the NF6 film was shown to be the maximum absorption of moisture absorption, which is 14.210.06%, should an occurrence of Nateglinide buccal films occur. This was caused by the presence of HPMC and a high concentration of carbopol. The NF10 film showed an extremely high estimation of moisture loss, 10.060.06. This may have occurred due to the proximity of PVP and the absence of carbopol. All of the films showed the passage of water as water vapour, and the water transmission test confirmed this. The NF10 film had the highest transmission of water vapour, which was about 9.980.59, while the NF5 film had the lowest transmission of water vapour, which was around 3.760.08 among all films. A polymer's swelling rate behaviour provides a relative moisture retention limit and also allows you to determine whether the films continue to preserve their integrity after absorbing moisture. Moreover, the presence of a water-solvent drug nearby may improve the matrix's surface wetting. Due to the presence of swellable polymers such HPMC, carbopol, and chitosan, the films started to swell within 9 minutes. After 60–120 minutes, the swelling reached its highest point. In contrast to the low levels of HPMC and carbopol, the films containing aberrant HPMC and carbopol had a high degree of swelling. The combination of carbopol and HPMC will determine this. More edoema was visible on the NF10 film than on the other films.

TABLE: 1. COMPOSITION OF NATEGLINIDE BUCCAL FILMS

Code of Formulation	Drug(mg)	Polymers (mg)				Solvents (ml)		
		HPMC	Chitosan	Carbopol	PVP	Ethanol (70% v/v)	Distilled water	PG (30% w/w)
NF1	20	2.5	-	-	0.5	5.5	4.0	0.6
NF2	20	-	2.5	-	0.5	5.5	4.0	0.6
NF3	20	-	-	2.5	0.5	5.5	4.0	0.6
NF4	20	1.0	0.5	0.5	0.5	5.5	4.0	0.6
NF5	20	0.5	1.0	0.5	0.5	5.5	4.0	0.6
NF6	20	0.5	0.5	1.0	0.5	5.5	4.0	0.6
NF7	20	1.5	0.25	0.25	0.5	5.5	4.0	0.6
NF8	20	0.25	1.5	0.25	0.5	5.5	4.0	0.6
NF9	20	0.25	0.25	1.5	0.5	5.5	4.0	0.6
NF10	20	2	0.5	-	0.5	5.5	4.0	0.6
NF11	20	-	2	0.5	0.5	5.5	4.0	0.6
NF12	20	0.5	2	-	0.5	5.5	4.0	0.6
NF13	20	-	0.5	2	0.5	5.5	4.0	0.6
NF14	20	2	-	0.5	0.5	5.5	4.0	0.6
NF15	20	0.5	-	2	0.5	5.5	4.0	0.6

TABLE: 2. EVALUATION OF NATEGLINIDE BUCCAL FILMS

F. Code	Thickness (mm)	Weight (mg)	Fold. end	Surface pH	PMA	PML	% S	Q
NF1	0.48±0.02	178.23±0.91	320±5.013	6.73±0.005	5.21±0.07	5.97±0.12	120.9±0.9	8.39±0.35
NF2	0.40±0.01	171.18±0.91	300±3.043	6.79±0.005	7.32±0.04	5.14±0.72	99.6±0.69	5.46±0.34
NF3	0.47±0.01	176.53±0.80	315±1.027	6.71±0.015	9.24±0.09	4.74±0.10	118.4±0.72	5.95±0.34
NF4	0.39±0.01	168.31±0.58	298±6.011	6.64±0.050	10.32±0.11	4.14±0.20	124.2±0.99	4.38±0.35
NF5	0.35±0.02	166.37±0.80	281±4.037	6.60±0.015	12.13±0.09	4.08±0.03	122.4±0.6	3.76±0.08
NF6	0.41±0.01	172.12±1.00	318±5.019	6.69±0.03	14.21±0.06	3.88±0.02	128.0±0.85	5.18±0.32
NF7	0.40±0.21	170.53±0.80	310±1.093	6.70±0.03	7.86±0.27	6.44±0.10	120.4±0.72	8.67±0.35
NF8	0.38±0.05	169.31±0.48	296±6.067	6.82±0.015	6.18±0.13	7.13±0.08	114.2±0.99	9.27± .52
NF9	0.36±0.02	166.37±0.20	320±4.033	6.81±0.005	5.34±0.12	9.12±0.07	130.4±0.6	9.37±0.43
NF10	0.39±0.01	168.12±1.00	320±5.072	6.77±0.001	4.12±0.13	10.06±0.06	125±0.85	9.98±0.59
NF11	0.34±0.01	165.17±1.10	286±2.082	6.67±0.003	3.85±0.22	9.05±0.04	128.6±0.4	9.46±0.59
NF12	0.39±0.01	169.27±1.10	294±1.076	6.74±0.008	3.93±0.33	8.04±0.08	123.2±0.63	9.56±0.59
NF13	0.38±0.01	172.37±0.60	304±3.093	6.67±0.005	11.26±0.24	5.72±0.01	77.4±0.7	5.91±0.38
NF14	0.36±0.01	171.07±0.90	305±2.081	6.63±0.005	9.89±0.22	6.13±0.02	72.51±0.6	6.32±0.20
NF15	0.32±0.01	168.43±0.50	302±2.028	6.61±0.017	7.02±0.06	7.45±0.52	69.56±0.65	6.94±0.31

BUCCOADHESIVE STRENGTH

For bioadhesion, it was believed that the attach adaptability and surface charge thickness were necessary, however the resident time was mostly determined by the polymer's rate of dissolution. The films containing carbopol were shown to have the strongest bioadhesive properties, possibly as a result of its anionic makeup. The Nateglinide films' bioadhesive properties made it easy to retain them in the buccal cavity. It was observed that HPMC particles were more numerous, smaller, and had a larger surface area that could make contact with the body fluid film. The improvement in the bioadhesive quality upon PVP collection may be attributed to the design of the hydrogen bond and van der Waal forces. In NF10 film, the strongest buccoadhesive property was attained.

TABLE: 3. BUCCOADHESIVE STRENGTH OF NATEGLINIDE FILMS

Code of formulation	Buccoadhesive strength in g
NF1	14.7±0.014
NF2	11.9±0.042
NF3	15.6±0.831
NF4	17.8±0.036
NF5	26.9±0.324
NF6	32.6±0.154
NF7	14.1±0.062
NF8	12.9±0.156
NF9	17.6±0.289
NF10	35.9±0.213
NF11	24.5±0.376
NF12	32.3±0.082
NF13	32.6±0.831
NF14	33.4±0.682
NF15	31.2±0.471

MECHANICAL STRENGTH

At the time of organisation, the mechanical quality of the film will play a crucial role in demonstrating the comfort and flexibility of the buccal cavity. Once the concentration exceeded the acceptable range, any polymer-polymer connections were eliminated by the addition of additional plasticizer atoms to the free space between the polymer chains. This could be the reason why, after the consolidation of greater plasticizer fixations, the prolongation was reduced. Moreover, the overuse of plasticizer reduced the amount of free space and impeded the growth of the polymer chain.

TABLE: 4. MECHANICAL STRENGTH OF NATEGLINIDE FILMS

Code of formulations	Mechanical strength in kg/mm^2
NF1	3.63±0.253
NF2	4.81±0.258
NF3	4.61±1.162
NF4	8.12±1.031
NF5	8.97±1.803
NF6	9.56±1.056
NF7	4.01±0.097
NF8	5.86±1.749
NF9	7.93±1.381
NF10	11.81±0.914
NF11	7.93±0.437
NF12	9.62±1.936
NF13	8.71±1.038
NF14	10.49±1.171
NF15	8.72±1.948

EX-VIVO RESIDENCE TIME

Table shows the results of describing the films for ex-vivo residence time using sheep mucosa. This test replicates the polymer's sticky limit when it is used in formulation. Every single movie listed a stay time ranging from 4.02 to 10.92 hours. All of the polymers used were hydrogels that shaped hydrophilic networks and swelled to adhere to the surface of physiological fluids. The duration of ex-vivo stay is specifically related to the swelling file. With delayed drug release, the polymer HPMC and chitosan showed the most extreme residence times, whereas NF10 showed the longest residence times.

TABLE: 5. EX-VIVO RESIDENCE TIME OF FORMULATIONS NF1 TO NF15

Code of formulations	Ex-vivo residence time (hr)
NF1	4.02 ± 1.382
NF2	5.13 ± 0.932
NF3	6.27 ± 1.173
NF4	7.19 ± 1.845
NF5	6.54 ± 0.049
NF6	6.57 ± 2.028
NF7	5.59 ± 1.047
NF8	6.12± 0.917
NF9	8.58 ± 1.835
NF10	10.57 ± 1.481
NF11	6.39± 0.096
NF12	7.57 ± 1.029
NF13	8.54 ± 1.931
NF14	7.53 ± 1.692
NF15	6.58 ± 1.041

IN-VITRO DRUG RELEASE

The Nateglinide release in complete formulations showed a striking contrast. The regression value supported the in-vitro drug discharge and Higuchi's plot findings that the release of the medication occurred in a zero-order fashion (r). Because carbopol was in an ionised state, the polymer-shaped system became noticeably slack and a high drug release was observed. The presence of PVP reduced the medication release caused by an increase in polymer swelling, and as a result, barrier impact increased, resulting in a decrease in drug discharge, so reducing the release of medicine. Coatings with lower concentrations of HPMC or carbopol released the drug in vitro only marginally more than formulations with larger concentrations of those polymers, which is due to consistency improvement brought on by the hydrophilic HPMC and carbopol's gelling concept. The pharmaceutical release is reduced as a result of formulations' expanded uniformity. Although some formulations' drug release was observed in larger groups over 10 to 12 hours, several of these films had inadequate ex-vivo residence

times; as a result, the films displayed attractive release in the two tests designed for further testing. The NF10 film showed 99.6 0.550 on 12 hours, while the NF9 film showed 96.2 1.49. In the formulation, drug release from NF1 to NF9 decreased as polymer concentration increased, and the NF10 film showed the greatest release. Furthermore, it was discovered that films created by combining higher concentrations of carbopol and chitosan revealed that delayed medicine release, signifying an improved matrix character of polymers.

CONCLUSION

Transmucosal drug delivery, which encompasses drug distribution through the mucosal linings of the oral, nasal, rectal, vaginal, and ocular cavities, is the term used to describe drug delivery through mucosal linings. The mucosal route of drug absorption avoids the gastrointestinal tract and hepatic portal system and increases the bioavailability of medications with a high first pass metabolism. The prevention of pre-systemic clearance in the GI tract and the bypassing of the hepatic first pass impact are two advantages this approach has over oral delivery for a systemic effect. Bioadhesive polymers and muco adhesive polymers Adhesive polymers have been used to improve drug delivery system retention at the absorption site. These polymers continue to adhere to the biological tissue, lengthen the drug delivery system's stay at the application site, and enhance the gradient of concentration, which heightens medication absorption. In this way, the mucosal route increases bioavailability by bypassing first pass metabolism. Therefore, using both the mucosal route and sticky polymers will increase the drug's bioavailability via improving absorption. Muco sticky polymers can be used to achieve this. According to a typical definition, muco adhesion is "Adherence of polymeric material to the mucosal tissue." According to Longer and Robinson, "attachment of a synthetic or natural molecule to mucus" is what the term "bioadhesion" means.

The oral mucosal route is chosen among all mucosal drug administration methods due to its simplicity. Although some molecules are commercialized through the nasal route, it has lost some of its appeal due to the possibility of discomfort. Because of the nasal mucosal route, the ciliary activity of the nasal cavity was irreversibly impaired. The mucus discharge of the nasal mucosa varies greatly across and among subjects, which affects how well the medicine is absorbed through the nasal route. Due to poor patient compliance, the ocular, vaginal, and rectal routes were only favored for local application rather than systemic use.

Although sublingual mucosa is more permeable than buccal mucosa, it cannot be used for transmucosal distribution since there isn't enough expanse of smooth muscle or immobile mucosa, and placing the device is challenging because saliva is constantly washing it. Periodontal disorders, toothaches, and bacterial and fungal infections are all treated locally in the oral cavity. Oral mucosa has a high blood supply, is moderately permeable, and recovers quickly from injury or stress. Pregastric absorption from the tissues of the oral cavity decreases the dose and dose-dependent side effects by avoiding first pass metabolism and improving bioavailability. Patient compliance can be increased by reducing the frequency of administration. Oral mucosa, in contrast to other mucosal sites, is frequently exposed to various external substances; as a result, it is anticipated to be relatively robust and less likely to experience irreparable damage brought on by a medicine or dosage form.

Intraoral dosage form or intraoral delivery system refers to the dosage form intended to release the active component in the oral cavity. Using the highly permeable oral mucosal tissue, drugs can be delivered either systemically (Oral Transmucosal Delivery, or OTD), or locally (Oral Mucosal Delivery, or OMD), to nearby tissues.

Three types of intraoral medication administration are recognized: (i) Buccal delivery, in which the medication is injected into the cheeks through the buccal mucosa, a mucous membrane. Local delivery, in which the medicine is administered directly into the oral cavity, and sublingual delivery, in which the drug enters the systemic circulation through the mucosal membranes covering the mouth's floor. Due to the buccal mucosa's strong blood supply, easy accessibility, and relative permeability, it is a very appealing route for systemic drug administration within the oral mucosal cavity.

The buccal mucosa is most adapted for both local and systemic medication delivery. The buccal route was used to distribute a variety of dosage forms, such as semisolids, patches, compacts, pills, sprays, gels, films, or bilayered and multilayered devices. All in all, films demonstrated better patient compliance than other dose forms due to their tiny size and lower thickness. Because they are more flexible and comfortable than buccal tablet formulations, these might be preferable. In addition, compared to oral gels, which are rapidly washed away and eliminated by saliva, film formulations would have a prolonged residence time on the mucosa. When opposed to ointments and gels, buccal films will also guarantee proper drug dosing.

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