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A STUDY ON FORMULATION AND EVALUATION OF MUCOADHESIVE CUPS

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ABSTRACT

The buccal mucosa's epithelial cells are encircled by mucus, an intercellular ground substance that can range in thickness from 40 m to 300 m. The majority of mucus is produced by the minor salivary glands and sublingual glands, which are also essential for preserving the mucin layer over the oral mucosa. The goal of the current study was to create a novel mucoadhesive drug delivery system for nateglinide. The goal of this work was to transport the medicine unidirectionally to the target locations in order to create a non-invasive dosage form that is more efficient and has improved bioavailability. With the aid of mucoadhesive polymers and a variety of mechanisms, bioadhesive or mucoadhesive systems stick to the mucosal surface for an extended period of time. Polyacrylic acid (carbopol polycarbophil), chitosan, (Polymethyl vinyl ether/maleic anhydride copolymers), cholestyramine, HPMC, sephadex, sodium alginate, PEG, dextran, sucralfate, poly (alkyl cyanoacrylate), and polylactic acid are some of the mucoadhesive polymers utilised to create such systems. The electronic theory, which proposed an attractive electrostatic force between the bioadhesive substance and glycoprotein mucin network, is one of many ideas used to explain the mechanism of mucoadhesion. On the other hand, adsorption theory claims that mucoadhesion is aided by secondary forces such as hydrogen bonding and van der Waals forces. Wetting theory is based on the development of close contact between bioadhesive polymers and mucus layers, whereas diffusion theory proposes physical entanglement of mucin strands with flexible polymer chains. The GIT's rapid mucus production makes it challenging to keep polymers' effective mucoadhesion in place. The stomach's tendency to be hydrated also lessens a polymer's ability to adhere to living things.

KEY WORDS: Formulation and Evaluation, Mucoadhesive Cups, Diffusion.

INTRODUCTION

With the only purpose of creating a dosage form that is effective, patient-friendly, stable, affordable, and delivers the medicine as close as possible to the intended target with the least amount of side effects, pharmaceutical dosage form creation is a combination of art and science. The development of innovative medication delivery systems has frequently replaced traditional methods of drug administration. Pharmaceutical businesses are currently looking for novel drug delivery systems and creative dosage forms because they are strategic tools for growing markets and indications, lengthening product life cycles, and creating new opportunities. No longer a theory, NDDS. It is a truth, as evidenced by the fact that NDDS account for roughly 13% of the present worldwide pharmaceutical market. Transmucosal drug delivery saw the second-highest growth among NDDS in the last five years (171%), while market growth as a whole was 106%.

The creation of several new medications, including peptides, proteins, polysaccharides, nucleic acids, and other compounds with improved pharmacological activity and site specificity, was made possible by the quick advancements in molecular biology and gene technology. However, these medications' poor oral absorption as a result of substantial presystemic metabolism and instability in an acidic environment is the principal barrier to oral administration. As a result, it is often necessary to administer medications via the parenteral route, which is extremely expensive and not as patient-friendly. This prevents many pharmaceuticals from realizing their full therapeutic potential. Additionally, the parenteral method is the most dangerous because to the possibility of infection, extravasations, and allergy. Due to the parenteral route's significant limitations and low drug bioavailability, innovative non-invasive alternative drug delivery techniques are being researched.

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 bioavailabilities 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.

RESEARCH METHODOLOGY

Due to their inability to restrict and confine the delivery systems in specific parts of the buccal and gastrointestinal (GI) tract, oral controlled release systems have presented a challenge to researchers in the planning stage. In order to ensure continued beneficial action and, as a result,

an increasing interest in their development, controlled drug delivery systems aim to maintain plasma concentration of pharmaceuticals inside the therapeutic window for a longer time period. Regular oral communication's main drawback is its lack of place specificity. One of the site-specific delivery methods for delivering pharmaceuticals to the stomach, digestive system, or oral cavity is mucoadhesive medication delivery.

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.

DRUG-POLYMER COMPATIBILITY BY PHYSICAL OBSERVATION

The 1:1 mixture of active ingredients and excipients were stored in sealed vials with elastic plugs for a period of a month in accelerated air conditions (40°C/75% RH). For changes in physical qualities, the active component and blends were monitored at the end of the first, second, and fourth weeks.

FORMULATION & EVALUATION OF MUCOADHESIVE TABLETS

In three processes, mostly using sticky cups, core tablets, and mucoahesive tablets, nateglinide mucoahesive tablets were created.

PREPARATION OF ADHESIVE CUPS

Wet granulation was used to create the sticky cups filled with granules. The separate mucoadhesive substance was combined with microcrystalline cellulose for the elaboration of adhesive cups, 10% w/v PVP solution was used as the granulating agent, and the mixture was then run through sieve #18. Granules were sieved via sieve #22 and dried in a tray dryer at 50°C for 6 hours. The powder, saccharin, and vanillin were added to the granules in calculated amounts.

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RESULTS AND DISCUSSION

FORMULATION AND EVALUATION OF MUCOADHESIVE CUPS

Several proportions of mucoadhesive polymers were used to create mucoadhesive cups, which serve as a barrier against medication release through diffusion. Common materials like talc (1%), polyvinyl pyrrolidone (5% w/v), and other lubricants were utilised to make the mucoadhesive cups. Table-1 displays the mucoadhesive cups' chemical make-up. The prepared mucoadhesive cups were evaluated using a variety of physicochemical criteria. Table -1 showed the granules' physical characteristics.

TABLE:1. COMPOSITION OF MUCOADHESIVE CUPS

Form. Code	**Polymer compositions (%)**				
	Carbopol	**HEC**	**CMCS**	**HPMCK15**	**Sod.Alg**
MAC1	100	-	-	-	-
MAC2	-	100	-	-	-
MAC3	-	-	100	-	-
MAC4	-	-	-	100	-
MAC5	-	-	-	-	100
MAC6	75	25	-	-	-
MAC7	75	-	25	-	-
MAC8	75	-	-	25	-
MAC9	75	-	-	-	25
MAC10	75	-	-	-	-

MAC11	25	75	-	-	-
MAC12	-	75	-	25	-
MAC13	-	-	75	-	25
MAC14	-	-	75	-	-
MAC15	50	50	-	-	-
MAC16	50	-	50	-	-
MAC17	50	-	-	50	-
MAC18	50	-	-	-	50
MAC19	50	-	-	-	-
MAC20	25	-	75	-	-

TABLE: 2. PHYSICAL AND FLOW PROPERTIES OF GRANULES

Code	**Derived properties Mean± SD(n=3)**		**Flow properties**		
	Bulk density (g/ml)	**Tapped density (g/ml)**	**Angle of repose (^{o})**	**Carr's index (%)**	**Hausner's ratio**
MAC1	0.43±0.010	0.49±0.015	29.45±0.30	12.24	1.139
MAC2	0.44±0.013	0.50±0.020	28.21±0.39	12	1.136
MAC3	0.49±0.015	0.56±0.010	25.97±0.68	12.5	1.142
MAC4	0.47±0.015	0.52±0.015	23.21±0.96	9.6	1.106
MAC5	0.43±0.020	0.49±0.030	28.94±0.73	12.24	1.139
MAC6	0.42±0.010	0.46±0.006	24.25±0.36	8.69	1.095

MAC7	0.45±0.025	0.53±0.025	31.21±0.29	15.09	1.177
MAC8	0.45±0.010	0.51±0.017	23.87±0.40	11.76	1.133
MAC9	0.41±0.010	0.45±0.025	25.17±0.34	8.8	1.097
MAC10	0.44±0.015	0.51±0.032	26.78±0.63	13.72	1.159
MAC11	0.40±0.020	0.47±0.010	23.93±0.46	14.89	1.175
MAC12	0.41±0.020	0.47±0.015	30.21±0.27	12.76	1.14
MAC13	0.45±0.015	0.51±0.020	25.87±0.39	11.76	1.13
MAC14	0.42±0.017	0.48±0.020	26.98±0.54	12.5	1.14
MAC15	0.45±0.015	0.50±0.020	27.81±0.28	10	1.11
MAC16	0.42±0.017	0.42±0.050	25.77±0.35	8.69	1.09
MAC17	0.43±0.082	0.47±0.014	24.08±0.42	8.51	1.09
MAC18	0.46±0.01	0.51±0.01	24.31±0.24	9.8	1.10
MAC19	0.41±0.04	0.47±0.02	25.94±0.16	12.76	1.14
MAC20	0.42±0.03	0.48±0.03	26.35±0.19	12.5	1.14

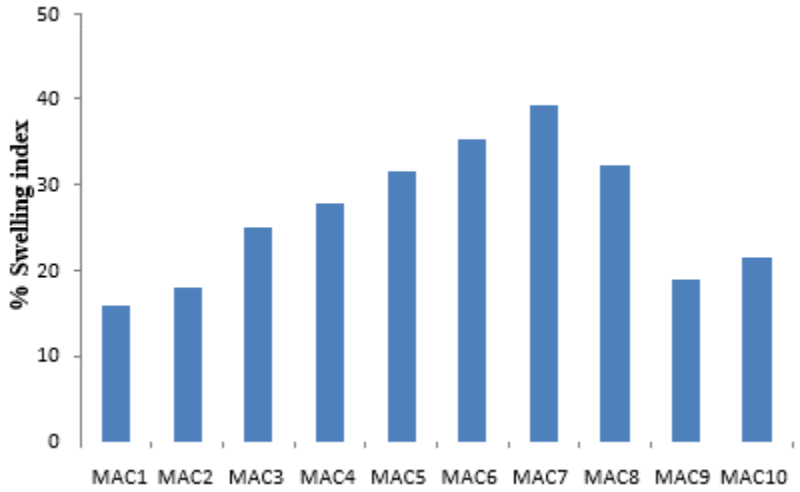
SWELLING INDEX

At the end of 6 hours, the swelling profiles of the adhesive cups in MAC18 were high and shifted between the sticky cups. The proximity of water soluble polymers may be the source of the increased swelling list. It has been stated that the polymer's ability to swell is essential for the performance of its mucoadhesive properties. In 6 hours, a higher rate of swelling was obtained, followed by the polymer starting to gradually disintegrate in the medium. When compared to HPMC and carbopol, sodium CMC is less thick, which results in weaker

molecular interactions. Table -3 shows the findings of the swelling properties at various time periods.

TABLE: 3. SWELLING INDEX OF MUCOADHESIVE CUPS

Code	Swelling Index (%)
MAC1	15.9±0.034
MAC2	17.9±0.327
MAC3	25.1±1.843
MAC4	27.8±2.092
MAC5	31.6±1.963
MAC6	35.3±0.043
MAC7	39.2±1.172
MAC8	32.2±0.834
MAC9	18.9±2.032
MAC10	21.5±1.732
MAC11	31.2±0.398
MAC12	45.7±1.032
MAC13	54.5±2.081
MAC14	59.1±2.097
MAC15	60.8±2.173
MAC16	58.8±0.939
MAC17	64.1±0.832
MAC18	66.8±1.749
MAC19	40.4±1.831
MAC20	49.9±2.064



ADHESIVE CUPS

FIGURE: 1. SWELLING PERCENTAGE OF MUCOADHESIVE CUPS.

MUCOADHESIVE STRENGTH

The mucoadhesive strength was evaluated using freshly collected sheep mucosa as the substrate. The adhesive cups made with sodium alginate and carbopol displayed somewhat better force of adhesion and bond strength than the other polymers. Comparing MAC2, MAC4, and MAC8, MC18 had greater mucoadhesive strength.

TABLE: 4. MUCOADHESIVE STRENGTH OF MUCOADHESIVE CUPS

Code	Mucoadhesive Strength (g)
MAC1	32.3±1.024
MAC2	40.2±1.723
MAC3	34.1±0.972
MAC4	42.4±1.632
MAC5	26.8±0.641

MAC6	23.9±1.895
MAC7	27.1±1.532
MAC8	38.8±1.628
MAC9	37.4±1.936
MAC10	41.3±0.942
MAC11	24.1±1.751
MAC12	21.7±1.979
MAC13	26.8±1.545
MAC14	25.1±2.896
MAC15	21.9±0.846
MAC16	31.6±1.542
MAC17	32.7±2.875
MAC18	33.1±1.084
MAC19	30.5±2.027
MAC20	27.8±2.811

EX-VIVO RESIDENCE TIME

Using sheep mucosa, the mucoadhesive cups were tested for ex-vivo residence time. The results are arranged in table-5. Residence time is the crucial amount of time needed to successfully separate the cup from the mucosal surface without losing credibility. This test is used to determine the polymer's maximum adhesive strength. Because the polymers used were hydro gel framing hydrophilic matrix and expanded to follow the physiological fluid surface, each cup showed a living arrangement time of 2.16 to 5.52 hours. The ex-vivo residence time associated with list swelling. In order to define controlled release systems, sodium alginate and the polymer carbopol were found to have the most severe residence times with delayed drug discharge. The residence duration was seen to slightly decrease when the concentration of

carbopol and hydroxy ethyl cellulose increased. Due to decreased swelling in phosphate buffer pH 6, this occurred.

TABLE: 5. EX-VIVO RESIDENCE TIME OF MUCOADHESIVE CUPS

Mucoadhesive cups	Residence time (hours)
MAC1	5.34±0.42
MAC2	5.52±0.61
MAC3	4.21±0.05
MAC4	5.42±0.82
MAC5	3.58±0.02
MAC6	3.35±0.82
MAC7	3.43±0.18
MAC8	5.36±0.82
MAC9	5.12±0.47
MAC10	5.28±0.45
MAC11	2.35±0.78
MAC12	2.31±0.28
MAC13	2.16±0.34
MAC14	2.39±0.82
MAC15	3.11±0.07
MAC16	2.51±0.21
MAC17	2.56±0.04
MAC18	3.48±0.82
MAC19	4.21±0.12
MAC20	3.51±0.03

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TABLE 6.: IN-VITRO SHEAR, PEEL AND TENSILE STRENGTH OF MUCOADHESIVE CUPS

Code	Shear strength		Peel strength		Tensile strength	
	Force of Adhesion (N)	Bond strength (N/m^2)	Force of Adhesion (N)	Bond strength (N/m^2)	Force of Adhesion (N)	Bond strength (N/m^2)
MAC1	0.0221	3471.32	0.0282	3502.83	0.0342	3638.43
MAC2	0.0234	3561.62	0.0341	3599.23	0.0355	3599.89
MAC3	0.0303	3982.43	0.0289	3825.56	0.0378	4126.24
MAC4	0.0314	3481.26	0.0278	3508.43	0.0353	3642.13
MAC5	0.0319	3671.31	0.0314	3696.21	0.0298	3762.72
MAC6	0.0321	3572.18	0.0287	3612.34	0.0372	3872.61
MAC7	0.0306	3870.43	0.0289	3798.24	0.0365	3981.23
MAC8	0.0344	3508.17	0.0351	3563.21	0.0348	3689.14
MAC9	0.0363	3983.36	0.0392	3871.44	0.0381	3972.26
MAC10	0.0375	3906.27	0.0396	3985.32	0.0372	3851.18
MAC11	0.0349	3362.31	0.0332	3475.32	0.0372	3672.28
MAC12	0.0282	2981.32	0.0279	2896.27	0.0323	2751.37
MAC13	0.0291	3751.32	0.0369	3798.34	0.0386	3864.29
MAC14	0.0347	3671.24	0.0362	3586.28	0.0369	3794.15
MAC15	0.0378	3586.15	0.0358	3407.21	0.0336	3653.41

MAC16	0.0395	3924.32	0.0391	3896.36	0.0393	3986.32
MAC17	0.0322	3586.27	0.0356	3489.42	0.0398	3521.27
MAC18	0.0381	3471.48	0.0339	3782.61	0.0377	3786.34
MAC19	0.0393	3762.03	0.0368	3672.25	0.0342	3598.32
MAC20	0.0326	3497.11	0.0336	3754.26	0.0348	3971.35

CONCLUSION

The goal of the current study was to create a novel mucoadhesive drug delivery system for nateglinide. The goal of this work was to transport the medicine unidirectionally to the target locations in order to create a non-invasive dosage form that is more efficient and has improved bioavailability. The examination of a few mucoadhesive polymers derived from natural sources for mucoadhesive medication delivery was also included in this research project. Experiments were conducted to determine whether the chosen polymers could be used in the creation of mucoadhesive tablets and buccal films for Nateglinide. Drug-excipient compatibility tests were carried out using differential scanning colorimetry and infrared technology. The preparation of mucoadhesive drug delivery systems in the form of tablets and films, along with ex vivo mucoadhesion, permeation studies, pharmacokinetic evaluations of optimised formulations, and stability studies on optimised formulations developed in accordance with International Conference on Hormonization (ICH) guidelines, were evaluated. The substantial perception, infrared, and differential scanning colorimetry examinations that were used to support the drug-polymer connection theories suggested that there was not a significant relationship between the medicine and polymers. As a result, the medication and polymer materials selected were perfectly suitable for the construction of Nateglinide buccal films and mucoadhesive tablets. The residence times for all of the tablet (mucoadhesive cup) designs ranged from 2.16 to 5.52 hours. Despite the fact that all of the used polymers were hydrogels with hydrophilic lattices, they swell and stick to the mucus surface. The optimal formulation for a controlled release

system was found to be sodium carboxymethyl cellulose and polymer carbopol, which demonstrated a maximum ex-vivo residence time of 5.52 hours with sustained drug release. This calculation was based on the swelling index.

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